SYMPOSIUM

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Prenatal programming of newborn and infant telomere length

Rationale/statement of the problem: Substantial evidence suggests conditions in intrauterine life may play a critical role in subsequent health and disease susceptibility related outcomes (i.e., the concept of fetal or developmental programming of health and disease). The elucidation of biological mechanisms underlying these effects is an area of active investigation. We suggest that telomere biology may represent a novel mechanism underlying the effects of a disparate set of suboptimal intrauterine exposures on various health and disease risk phenotypes. From an evolutionary-developmental perspective, energy substrate availability (i.e., nutrition) and challenges that have the potential to impact the structural or functional integrity and survival of the organism (i.e., stress) likely represent the most important environmental considerations underlying natural selection and developmental plasticity. Maternal stress and nutrition in pregnancy therefore represent attractive candidate processes in the context of fetal programming of telomere biology. Our previous work has established an important role for prenatal stress and stress-related processes in adult telomere biology.
Methods: In two longitudinal birth cohorts, stress- and nutrition-related processes were assessed during pregnancy and telomere length (TL) was subsequently measured in newborns (cord blood) and infants (buccal cells).
Results: (1) Among the nutrition-related factors, maternal lower folate levels (an essential methyl donor) and higher triglyceride concentrations in early pregnancy were significantly and independently associated with shorter newborn TL. (2) Among psychosocial stress-related measures, higher maternal pregnancy-specific stress was associated with shorter newborn TL. (3) Maternal estrogen (E3) levels during early pregnancy were associated with longer infant TL.
Conclusion: Taken together, our findings provide the first evidence in humans that maternal nutrition and stress-related processes during pregnancy may exert a programming effect on the newborn and infant telomere biology system. *In utero* telomere biology represents a potential molecular mechanism whereby different exposures in this critical developmental period *before* birth could impact subsequent health and disease susceptibility related outcomes over the life span, including aging and longevity.

Keywords: teleomere biology; teleomere length; newborn; health; stress; aging

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Childhood trauma and telomere maintenance

Rationale/statement of the problem: Stress in early life is known to have a powerful direct effect on poor health in later life. This direct effect requires one or more underlying mechanisms that can maintain it across the life-course. It is therefore essential to characterize the biological mechanisms through which children may acquire such lasting vulnerability to disease, namely, the mechanisms of biological embedding. One plausible mechanism may lie in changes to DNA. New research suggests that stress exposures can accelerate the erosion of DNA segments called telomeres.
In the past 2 years, six studies provided support for an association between telomere length (TL) and childhood stress. Although these studies advance understanding of the link between childhood stress and TL, almost all studies have relied on adult measures of TL and retrospective recall of stress years after the stress was experienced raising important questions about the true nature of these findings. Interpretation of findings from cross-sectional studies of TL is ambiguous in light of recent longitudinal analyses of repeated TL measurements. These recent findings indicate that the temporal process of telomere erosion is more complex than initially assumed, and that repeated measures (not just length at one time point) are needed to measure true telomere erosion in individuals who are experiencing stress. Moreover, given the elapsed time between the putative stress exposure and the measurement of

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TL, it has not been clear whether telomeres began eroding during stress exposure or whether erosion occurred years later, possibly promoted by the sequelae of childhood stress or other intervening variables.
In our study, we used a longitudinal design to test the effects of violence exposure during childhood on telomere erosion in a cohort of young children. We tested the hypothesis that cumulative violence exposure would accelerate telomere erosion in children while they experienced stress.
Method: Participants were 236 children (49% females; 42% with one or more violence exposures) recruited from the Environmental Risk (E-Risk) Longitudinal Twin Study, a nationally representative UK 1994–1995 birth cohort. Each child's mean relative telomere length was measured simultaneously in baseline and follow-up DNA buccal cells, using the quantitative PCR method for T/S ratio.
Violence was assessed as exposure to maternal domestic violence, frequent bullying victimization and physical maltreatment by an adult. We interviewed mothers (or the primary caregiver) about each exposure when the children were 5, 7, and 10 years of age and compiled a cumulative record of each child's exposure to violence. Nearly 54.2% ($N=128$) of the children were not violence exposed, 29.2% ($N=69$) were exposed to 1 type of violence, and 16.5% ($N=39$) were exposed to 2 or more types of violence.
To test the main hypothesis that violence exposure would accelerate telomere erosion between ages 5 and 10 years, we conducted ordinary least squares multiple regression analysis. The outcome variable was age-10 TL, controlling for baseline TL at age 5 years and sex, SES, and body mass index as covariates.
Results: We first examined the effect of each type of violence exposure on TL separately. Children exposed to domestic violence showed slightly accelerated telomere erosion from age 5 to 10, compared with children who had not been exposed to domestic violence, but this change was not statistically significant ($\beta=-0.059$, SE $=0.045$, $p=0.196$). Children exposed to frequent bullying victimization also showed slight but nonsignificant accelerated telomere erosion from age 5 to 10, compared with children who had not been exposed to bullying victimization ($\beta=-0.041$, SE $=0.037$, $p=0.274$). Children who were physically maltreated did show significantly accelerated telomere erosion from age 5 to 10, compared with children who had not been exposed to physical maltreatment ($\beta=-0.085$, SE $=0.037$, $p=0.022$).
Next, we tested the main hypothesis that cumulative exposure to violence will be associated with accelerated TL erosion. Children who experienced two or more kinds of violence exposure showed significant TL erosion from baseline to follow-up measurement compared with children who had one or no kinds of violence exposures ($\beta=-0.054$, SE $=0.023$, $p=0.020$)
Conclusion: This finding provides the first evidence that stress-related accelerated telomere erosion in buccal cells can be observed already at young age while children are experiencing stress. Children who experienced two or more types of violence exposure between age-5 baseline and age-10 follow-up measurements showed significantly more telomere erosion, even after adjusting for confounding factors. The results of the present study add weight to the hypothesis that exposure to stress in childhood can alter biological processes in relation to telomere erosion. Methodological strengths of this study include a longitudinal design with reliable and valid prospective assessments of multiple violence exposures during childhood and repeated measurements of TL during this same developmental period.

Keywords: early life trauma; teleomere length; teleomere erosion; violence

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From sadness to senescence: cellular effects of psychiatric syndromes

Rationale/statement of the problem: Major depressive disorder (MDD) and other serious mental illnesses are associated with high rates of comorbid medical illnesses. Many of these comorbid conditions are more typically seen in the aged, raising the possibility that these psychiatric illnesses are associated with accelerated aging. An emerging biomarker of cell aging and of increased risk of medical illness is leukocyte telomere length, and several studies have now characterized leukocyte telomere length in MDD and other psychiatric illnesses. Fewer psychiatric studies have characterized the activity of telomerase, an enzyme that can elongate and preserve telomeric DNA, or have investigated the biochemical mediators of accelerated telomere shortening.

Methods: Seven studies examining telomere length in MDD, three studies in schizophrenia, two studies in bipolar illness, two studies in PTSD, and one study in generalized anxiety disorder were reviewed, as were one study of telomerase activity in MDD and one study in schizophrenia. Additional studies in chronically stressed individuals and in individuals with histories of childhood adversity were also reviewed.
Results: Shortened leukocyte telomeres have been demonstrated in MDD, bipolar illness, schizophrenia, anxiety disorders, and post-traumatic stress disorder, although in some studies, only subgroups of patients (e.g., those with longer lifetime exposure to the illness, those with poor responses to treatment, or those with preexisting histories of childhood adversity) showed shortened telomeres. Leukocyte telomere shortening is correlated with peripheral indices of increased oxidative stress and increased immune activation. Two studies (one in caregivers with high depression ratings and one in unmedicated patients with MDD) reported elevated peripheral blood mononuclear cell (PBMC) telomerase activity, perhaps representing a compensatory attempt by the body to preserve endangered telomeres. Preliminary data in MDD suggest that relatively low telomerase activity before treatment, and greater treatment-associated increases in telomerase activity, are associated with better antidepressant responses. This, plus the preliminary observation that PBMC telomerase activity is directly correlated with hippocampal volume (by MRI) in MDD, support emerging preclinical data that telomerase has intrinsic neurotrophic and antidepressant effects.
Conclusion: Telomere shortening in MDD and certain other psychiatric conditions may, at least partially, reflect chronic exposure to inflammation and oxidation. As such, it may be a bellwether of increased medical risk, or it may play a more direct causal role in accelerated aging. The interplay of telomere integrity and telomerase activity may be an important determinant of psychiatric and medical outcome. Overall, the data are consistent with the view that MDD and certain other psychiatric illnesses have systemic manifestations beyond the brain and call into question the dichotomy of ''mental'' vs. ''physical'' illnesses.

Keywords: teleomere length; MDD; inflammation; oxidation; aging

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Stress and cellular aging: what's lifestyle got to do with it?

Rationale/statement of the problem: Chronic stressors across the life course predict accelerated pathogenesis of diseases of aging and early mortality. Telomere length, the DNA-based biomarker indicating cellular aging, is a mechanism of disease development, and shortens in a dose response fashion by duration and severity of life stressor exposures. Telomere length provides an important window in understanding a life span model of the accumulation of stress on aging. Self-reported perceived chronic stress and exposure to stressful life experiences during childhood and adulthood are related to short telomeres.
While the expectation that the accumulation of life stress leads to cellular senescence, most studies indicate cross-sectional associations between life stressors and telomere length. Findings suggesting longitudinal associations between life stressors and telomere shortening are best represented in studies associating self-reported early childhood traumatic experiences with short telomeres in adulthood. Adults reporting moderate-to-severe childhood maltreatment and stressful experiences, such as divorce and parental separation, are more likely to have significantly shorter telomeres than those reporting no childhood maltreatment. To date, only one study has prospectively demonstrated associations between traumatic experiences and telomere shortening. Five-year-old children exposed to two or more traumatic stressors, including maternal domestic violence, frequent bullying victimization and physical maltreatment by an adult, have shorter telomeres at age 10 compared with children exposed to less or no violent stressors.
No studies, however, indicate prospective effects of adulthood stressors on telomere shortening over time. Perhaps, as we suggest elsewhere, chronic stressor effects on biological pathways are rarely main effects, but rather an intricate interplay between life adversity and resiliency factors. Our work, and that of others, is increasing our understanding of how psychological stress resilience, social connections, and lifestyle may moderate relationships between life stressors and health. Here, we present evidence from two studies that support our proposed model that behavioral and psychosocial resiliency can buffer the effects of stress on telomere length, both cross-sectionally and prospectively. Cross-sectionally, we tested whether multisystem resiliency – defined as a composite of healthy emotion regulation, strong social connections, and being physically active – mitigates previously demonstrated

associations between concurrent depression diagnosis and telomere length. We found support for this model, which will be presented. In a second study we examined how a lifestyle composite might buffer stress-induced telomere shortening prospectively.

Methods: Two hundred sixty-one non-smoking women between the ages of 50 and 65 were recruited for a prospective study on telomere length change over the course of the year. Leukocyte telomere length (LTL) was assayed at baseline and 12-month follow-up. Perceived stress, typical dietary practices, sleep quality, and exercise levels were self-reported at baseline, 4 months, 8 months, and 12 month follow-up. Seventeen questions about life events that may have occurred in the previous year were asked at follow-up, including events such as divorce, death of a family member, and job loss. Health events were not included as they may confound effects of stressors on telomere biology. Women with histories of cancer, who were premenopausal, or did not have complete self-report data were excluded from these analyses, leaving a final sample of 196 women.

Results: Results indicated that perceived stress at baseline, perceived stress accumulated over the year, or accumulation of stressors over the year were unrelated to 12-month LTL, covarying baseline telomere length, age, BMI, and income level. However, findings do suggest significant interactions between markers of stress and a healthy lifestyle over the year composed of healthy dietary practices, sleep quality, and exercising. For those at one standard deviation below mean healthy lifestyle, baseline perceived stress ($b = -8.51$, SE $= 4.05$, $p = .04$) and accumulation of life stressors over the year ($b = -34.51$, SE $= 15.21$, $p = .02$), were significantly associated with shorter LTL at follow-up, covarying baseline telomere length, age, BMI, and income level. On the contrary, at one standard deviation above the mean of healthy lifestyle, stress markers were unrelated to telomere shortening over the year.

Conclusion: In summary, healthy lifestyle factors and psychosocial resiliency may interrupt a cascade of harmful effects that accelerate cellular aging, diminishing the impact that chronic psychological or objective life stress has on health. From conception to death, we are exposed to stressors. And while stressors may shape the manifestation of resiliency factors, leading to an interrelated cluster, our work suggests that psychosocial resources and lifestyle factors can add up to multisystem resiliency, providing increasing cellular buffering from life stress. Without attending to such interactions, stress effects are often masked and missed.

Keywords: stress; aging; teleomere length; resiliency

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Anxiety and depression in severely obese pregnancy: associations with gestational weight gain and birthweight

Rationale/statement of the problem: Obesity is associated with increased symptoms of anxiety and depression. We hypothesised that severe obesity in pregnancy would be associated with adverse psychological health, with effects on gestational weight gain (GWG) and baby birthweight (BWT). We aimed to study mood and birth outcomes among participants in a longitudinal study of severe obesity in pregnancy.

Methods: In this study, 140 severely obese (body mass index [BMI] (mean (SD)) 44.1 (4.1) kg/m^2) and 96 lean (BMI 22.6 (1.6) kg/m^2) pregnant women were recruited. Ethical approval and written, informed consent were obtained. Obese women were advised about healthy eating and weight maintenance. Serial weights were recorded and GWG calculated between 16 and 36 weeks' gestation. Women were asked to complete validated questionnaires to assess mood, including 'satisfaction with life', Hospital Anxiety and Depression Scale (HADS) and Spielberger State and Trait Anxiety in early (12–20 weeks' gestation) and late pregnancy (28–32 weeks' gestation). Term BWT (>37 weeks' gestation) was recorded ($n = 234$).

Results: Obese women were significantly less satisfied with life than lean women and had higher HADS depression and anxiety scores, and state and trait anxiety scores at both time points (all $p < 0.05$). Findings remained significant after adjustment for social class.Obese women had less GWG than lean women (5.3 (6.0) vs. 10.2 (3.7) kg, $p < 0.05$). About 23% of obese had more GWG than that prescribed in the Institute of Medicine guidelines. Offspring BWT was similar in obese and lean (3644 (515) vs. 3557 (505), $p =$ ns).

In lean, increased BWT was associated with higher BMI ($r = 0.68$, $p = 0.002$) and greater GWG ($r = 0.57$, $p = 0.005$). BWT was not related to BMI or GWG in obese. Higher HADS anxiety scores were associated with less GWG in lean ($r = -0.38$, $p = 0.01$) but more GWG in obese ($r = 0.33$, $p = 0.04$). Increased state anxiety was associated with lower BWT in early pregnancy in both groups ($p = 0.03$) with similar patterns in late pregnancy. BWT was not related to satisfaction with life or HADS scores.

Findings remained significant after adjustment for gender, delivery gestation, maternal smoking, social class, parity and ethnicity.

Conclusion: Severely obese pregnant women have more symptoms of anxiety and depression and are less satisfied with life than lean women. Increased anxiety in response to pregnancy is associated with lower BWT in all, but altered mood has differing associations with GWG in lean and obese. Understanding mood may help interventions to optimise GWG in severely obese women.

Keywords: anxiety; depression; pregnancy; gestational weight; birthweight; obesity

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Early-life stress, salivary HPA axis measures and cognitive profile in subjects with early psychosis

Rationale/statement of the problem: Although heritability is an important factor related to the onset of psychotic disorders, environmental factors also play a role. Early-life stress, which includes both prenatal stressful exposures and childhood maltreatment, has been suggested to have an impact on the developing brain. Cognitive alterations in schizophrenia and psychotic disorders have been described in several neuropsychological domains: attention, memory (verbal, visual and working memory), processing speed, reasoning and social cognition. Recent studies suggest that the hypothalamic–pituitary–adrenal (HPA) axis modulates cognitive functioning in patients with psychosis but that this association does not seem to be related to increased exposure to stressful events. We aimed to study whether early-life stress and the HPA axis are associated with a poorer cognitive performance in subjects with a psychotic disorder.

Methods: We studied 46 subjects with an early psychosis (aged 18–35 years), who were attending the Early Psychosis Program from Reus (HPU Institut Pere Mata, Spain). These subjects included three clinical populations: (1) first episode of psychosis (FEP, $N=17$); (2) critical period (CP, defined as a psychotic disorder >1 year of duration of illness, $N=17$); and (3) ultra high risk (UHR, subjects with prodromal psychotic symptoms, $N=12$). All subjects were assessed using a structured clinical interview (Schedules for Clinical Assessment in Neuropsychiatry and Comprehensive Assessment of at Risk Mental States) to obtain a clinical diagnosis. Obstetric history and perinatal stress were assessed retrospectively by parental recall, usually from the mother. Childhood maltreatment was assessed with the Childhood Trauma Questionnaire. The MATRICS Consensus Cognitive Battery was administered to explore neuropsychological functioning in seven domains: attention/vigilance, speed of processing, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. This cognitive battery gives T-scores corrected for age, sex and education level. Salivary samples at different times were obtained to determine cortisol levels. Three samples were obtained the same day of the neuropsychological assessment (before, during and after the battery). The area under the curve during these three assessments was calculated. Participants were also asked to collect salivary samples on a different day at home, on waking, 30′ post-waking, 60′ post-waking, 10.00 h, 23.00 h and at 10.00 h post-administration of 0.25 mg of dexamethasone the prior evening. The cortisol awakening response was calculated. Statistical analyses were performed with SPSS v.19.0. Spearman correlation was used to explore the association between CTQ scores, cortisol measures and cognitive domains. Wilcoxon test was used to compare ordinal and continuous data between groups. A p value <0.05 (bilateral) was considered to be significant. To compare those subjects with a poorer cognitive performance, for each cognitive domain we compared those subjects on the first quartile (25% of lower T-scores) with the rest of the sample (75% of greater T-scores).

Results: In relation to cognition, subjects with perinatal stress showed significantly poorer cognitive performance in the attention/vigilance domain ($r=-0.378$, $p=0.015$), whereas childhood maltreatment was associated with significantly lower scores in social cognition ($r=-0.365$, $p=0.017$). Perinatal stress and childhood maltreatment were not associated with differences in salivary cortisol levels. Salivary cortisol levels during the neuropsychological assessment, calculated with the area under the curve with respect to the ground, were associated with poorer visual learning ($r=-0.386$, $p=0.014$). A blunted cortisol-awakening response was associated with significantly poorer functioning in working memory ($p=0.022$).

Conclusions: Early-life stress and HPA axis measures are associated with a poorer cognitive functioning in subjects with early psychosis. However, cognitive domains seem to be affected differently by early-life stress and HPA axis measures: attention/vigilance by perinatal stress; social cognition by childhood maltreatment; visual and working memory by cortisol levels.

Keywords: early life stress; HPA-axis; saliva; cognition; early psychosis; cortisol

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Maternal pre-pregnancy obesity and child ADHD symptoms, executive function and cortical thickness

Rationale/statement of the problem: Increasing evidence suggests exposure to adverse conditions in intrauterine life may increase the risk of developing attention-deficit/hyperactivity disorder (ADHD) in childhood. High maternal pre-pregnancy body mass index (BMI) has been shown to predict child ADHD symptoms; however, the neurocognitive processes underlying this relationship are not known. The aim of the present study was to test the hypothesis that this association is mediated by alterations in child executive function and cortical development.
Methods: A population-based cohort of 174 children (mean age $=7.3 \pm 0.9$ (SD) years, 55% girls) was evaluated for ADHD symptoms, using the Child Behavior Checklist, and for neurocognitive function, using the Go/No-go Task. This cohort had been followed prospectively from early gestation and birth through infancy and childhood with serial measures of maternal and child prenatal and postnatal factors. In 108 children, a structural MRI scan was acquired and the association between maternal obesity and child cortical thickness was investigated using Freesurfer software.
Results: Maternal pre-pregnancy BMI was a significant predictor of child ADHD symptoms ($F_{(1,158)}=4.80$, $p=0.03$) and of child performance on the Go/No-go Task ($F_{(1,157)}=8.37$, $p=0.004$) after controlling for key potential confounding variables. A test of the mediation model revealed that the association between higher maternal pre-pregnancy BMI and child ADHD symptoms was mediated by impaired executive function (inefficient/less attentive processing; Sobel test: $t=2.39$ (± 0.002, SEM); $p=0.02$). Interestingly, after controlling for key potential confounding variables pre-pregnancy obesity was furthermore associated with region-specific thinner cortices, including regions previously reported to be thinner in children with ADHD, like the prefrontal cortex.
Conclusion: To the best of our knowledge, this is the first study to report the neurocognitive underpinnings of maternal pre-pregnancy BMI-related effects on child ADHD risk. These results add further evidence to the growing awareness that neurodevelopmental disorders such as ADHD may have their foundations very early in life.

Keywords: obesity; pregnancy; ADHD; BMI; executive function; cortical thickness

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The association between the acute psychobiological stress reactivity in second-trimester pregnant women and amniotic fluid cortisol and cortisone

Rationale/statement of the problem: Scientific evidence indicating that excessive stress during human pregnancy can have long-lasting effects on mother and child is increasing. But the underlying biological mechanisms remain elusive. Recent findings suggest a key role of the hypothalamic–pituitary–adrenal axis and the placental enzyme 11β-hydroxysteroid dehydrogenase Type 2 (11β-HSD2). This enzyme inactivates cortisol (F) to cortisone (E), thereby protecting the foetus from maternal F overexposure. Studies on pregnant rats show that placental 11β-HSD2 is up-regulated following acute maternal stress but impaired after chronic stress. Whether a similar mechanism exists in humans is unclear. Therefore, we investigated the acute stress response of salivary F (SalF) in second-trimester pregnant women undergoing amniocentesis and compared this response with amniotic fluid

F, E, and the E/(E+F) ratio as an index of placental 11β-HSD2 activity. Since 11β-HSD2 is also present in the adult salivary glands, we determined salivary E (SalE) and the SalE/(SalE+SalF) ratio, as a marker for salivary 11β-HSD2 activity as well and examined the association of these parameters with the amniotic fluid markers of stress.

Methods: Repeated saliva samples and an aliquot of amniotic fluid were collected from 34 healthy pregnant women (mean age = 37.5, SD = 3.9 years) undergoing amniocentesis for karyotyping. Changes in stress perception and state anxiety were monitored using questionnaires. Participants were re-invited for a control condition after receiving the inconspicuous test results of the amniocentesis.

Results: Compared to the control condition, the pregnant participants showed significant increases in psychological distress during the amniocentesis. SalF and SalE increased correspondingly while SalE/(SalE+SalF) decreased. SalF correlated positively with amniotic fluid E ($r = .38$, $p = .048$), and a stronger decrease in SalE/(SalE+SalF) was associated with increased amniotic fluid E/(E+F) ($r = .44$, $p = .02$).

Conclusions: The present results further our understanding of the maternal–foetal stress response considerably and suggest that during acute stress, maternal F is converted to E within the foeto-placental unit. This is most probably due to the activity of placental 11β-HSD2. Further investigation of the influence of chronic stress on the enzyme activity is essential.

Keywords: Prenatal stress; psychobiological stress reactivity; salivary cortisol; salivary cortisone; cortisol/cortisone ratio; amniotic fluid

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Lower maternal socioeconomic position increases placental glucocorticoid sensitivity and transfer

Rationale/statement of the problem: Lower socioeconomic position is associated with increased risk of morbidity and premature mortality from physical and mental disorders and confers similar "transgenerational" consequences on the offspring. The effects on the offspring appear initiated prenatally as lower socioeconomic position also increases risk of prematurity and small/large body size at birth. The biological mechanisms remain, however, elusive. We hypothesized that fetoplacental stress (glucocorticoid) hormone exposure might mediate the link, as we have found in first and second generation exposures to glucocorticoids in rodent pregnancy. We therefore examined associations between socioeconomic position and placental expression of placental genes involved in glucocorticoid exposure and transfer between the mother and fetus.

Methods: Biopsies of placental tissue were obtained from 62 healthy (mothers age 32.2±[SD] years), singleton, term pregnancies (37–42 gestational weeks) a maximum of 90 min after (vaginal or caesarian) delivery, snap frozen in liquid nitrogen, and stored at -80°C. Placental mRNAs encoding glucocorticoid receptor (GR) and 11-beta hydroxysteroid dehydrogenase 1 (HSD1) and 2 (HSD2), which regenerate and inactivate glucocorticoids respectively, were determined by real-time PCR. Level of education and occupational status of the mother, indices of socioeconomic position, were obtained from hospital birth records.

Results: Placental GR and HSD1 mRNAs increased with decreasing maternal education (unadjusted p values for linear trend = 0.04 and 0.02, respectively; p values adjusted for maternal age at delivery, fetal birth weight, and length of gestation = 0.08 and 0.02, respectively). Mothers with secondary education ($n = 23$) had 52.9% (95% CI = 6.2 to 99.6, $p = 0.03$, adjusted $p = 0.04$) higher placental GR mRNA and 81.9% (95% CI = 6.9 to 156.9, $p = 0.03$, adjusted $p = 0.03$) higher HSD1 mRNA compared with mothers with tertiary education (n = 39). The associations were similar with occupational status. Level of education and occupational status of the mothers were not associated with placental HSD2 mRNA (unadjusted/adjusted p-values > 0.58).

Conclusions: Lower socioeconomic position is associated with higher placental GR and HSD1 gene expression. This combination will both regenerate active glucocorticoids in placenta (with potential impact locally in placental cells and by spill-over on the fetus) and increase placental sensitivity to glucocorticoids. By analogy with preclinical mechanistic studies, this may have immediate offspring and transgenerational effects on cardiometabolic and neuropsychiatric risk but adds placental glucocorticoid sensitivity and regeneration as novel processes involved.

Keywords: socioeconomic position; morbidity; mortality; gene expression; transgenerational effects

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Sleep, diurnal cortisol, and survival among women with metastatic breast cancer

Rationale: In previous research, we found that flattened diurnal cortisol predicted early mortality with breast cancer, independent of other known risk factors, and this has since been confirmed among patients with lung cancer. In that study, loss of diurnal variation in cortisol was associated with self-reported awakenings during the night, implying an interaction with sleep disruption. This suggested that objective measures of sleep would clarify the relationship between disruption of circadian cortisol rhythms and sleep disturbance.
Methods: Here we recruited 101 women with metastatic breast cancer and 16 age- and socioeconomic status-matched controls. We measured sleep using full electroencephalographic (EEG), electro-oculographic, and electromyographic recordings in the clinical research center, where we were also able to draw blood samples throughout the night using a long IV line through a hole in the wall. Sleep measures were confirmed with two nights of home EEG recordings and 2 weeks of actigraphy.
Results: Among 63 for whom complete cortisol and sleep data are now available, we observed a phase shift in the relationship between the peak of cortisol and wake time such that patients woke earlier than their cortisol peak. Controls woke on average 1 h 20 min before the cortisol peak, whereas patients woke 1 h 54 min before. This control–patient difference was not statistically significant. However, among all subjects, there was a significant .38 correlation between diurnal cortisol slope and time from waking to the cortisol peak, such that those who woke earlier in relation to the cortisol peak had flatter cortisol slopes. Among the patients alone, the correlation was .43. This suggests that flattening of diurnal cortisol is associated with early morning waking. In the sample of 101, we found a relationship between misalignment of preferred and actual bedtimes and disease-free interval (DFI), the time from initial breast cancer diagnosis to date of metastasis. Shorter DFI is a strong predictor of reduced survival time. Going to bed earlier or later than preferred bedtime was associated with shorter DFIs, compared with aligned bedtime (HR = 3.25, 95% CI = 1.17–8.98, $p = .023$, and HR = 3.55, 95% CI = 1.33–9.45, $p = .011$, respectively). Mean DFI was 92.1 months (preferred), 39.8 months (earlier than preferred), and 54.1 months (later than preferred; Log Rank $p = .002$).
Conclusions: Thus waking ahead of the normal morning cortisol peak was related to flatter diurnal cortisol, and misalignment of preferred and actual sleep times was also associated with poor prognosis.

Keywords: sleep; cortisol; survival; cancer; metastatic breast cancer; prognosis

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Sleep and lipids in posttraumatic stress disorder

Background: Sleep disturbances are among the most common symptoms of posttraumatic stress disorder (PTSD). There is growing evidence that sleep fragmentation and short sleep duration are risk factors for hyperlipidemia, diabetes, obesity, and other risk factors for vascular disease. No work has examined the association of sleep with lipid metabolism in PTSD.
Methods: A cross-sectional 2×2 design (PTSD/control $\times$ male/female) included medication-free, nonobese, medically healthy subjects. The sample was comprised of 42 individuals with current chronic PTSD (52% female; *M* age = 30.81, SD = 6.55) and 45 age-and gender-matched controls without PTSD (51% female; M age = 30.04, SD = 8.07), ranging in age from 20 to 50 years. Sleep was monitored by diary for 1 week, and ambulatory polysomnography was performed over three nights on a research inpatient unit. Morning fasting lipids and adiponectin were measured after the second night of sleep.

Results: PTSD subjects had significantly elevated total cholesterol, very-low-density lipoprotein (VLDL) cholesterol, and triglycerides relative to controls (all p's $<.05$) controlling for body fat percentage as measured by dual-energy X-ray absorptiometry scan. Lower total sleep time was significantly associated with higher total cholesterol, VLDL cholesterol, and triglycerides in the total sample (and these relationships were strongest in the PTSD group). Total sleep time from sleep diary was directly correlated with total adiponectin ($r=.26$, $p=.04$) and high-molecular-weight adiponectin ($r=.27$, $p=.01$) in the full sample, and this relationship was strongest in the control group.
Discussion: The results suggest an association of sleep to cardiovascular risk factors in PTSD. Further research is needed to assess whether effective treatment of sleep in PTSD will favorably affect lipid metabolism.

Keywords: sleep; PTSD; lipids; cardiovascular risk; metabolism

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Lower peak numbers, blunted diurnal rhythms of immune cell distribution, and sleep disruption in metastatic breast cancer

Rationale: The peak number of protective immune cells measured in the blood at the zenith of their diurnal rhythm is a measure of their overall capacity for immunoprotection. Rhythmic diurnal changes in blood immune cell numbers reflect a redistribution of cells from the blood to other body compartments, and back into the blood. This redistribution may be critical for leukocyte maintenance and for the surveillance and effector functions of the immune system.
Methods: We investigated diurnal changes in absolute numbers of NK cells in patients with metastatic breast cancer (MBC) ($n=48$) and controls ($n=19$). Sleep quality was measured by home actigraphy. Leukocyte differentials were combined with flow cytometry to calculate NK cell numbers in whole blood samples obtained every 4h, starting 12 h (T1) after the midpoint of sleep on day 1 and ending 12 h (T7) after the midpoint of sleep on day 2.
Results: In agreement with the literature, control subjects showed peak blood NK cell numbers at T1, with a decrease to their diurnal trough at around the sleep midpoint (T4), followed by a return to diurnal peak numbers 12 h later. Compared to controls, patients with MBC showed significantly lower peak NK cell numbers ($p=0.039$), suggesting an overall decrease in NK-cell-mediated immunoprotection for patients. Interestingly, among patients, higher peak NK cell numbers were associated with a longer disease-free interval ($p=0.036$) and higher Karnofsky Performance Rating ($p=0.083$, trend), collectively indicating an association between higher peak NK cell numbers and better health and functional status. Compared to controls, patients with MBC also showed a smaller peak to trough decrease ($p=0.006$) that suggests reduced diurnal NK cell redistribution among different immune compartments which could also decrease immunoprotection. We further investigated the relationship between sleep disruption and damped NK cell rhythms in MBC patients. Higher average wake time after sleep onset was associated with a smaller peak to trough decrease ($R=-0.38$, $p=0.006$). The average number of awakenings was also associated with a smaller peak to trough decrease ($R=-0.36$, $p=0.014$). In contrast, average sleep efficiency was associated with a larger peak to trough decrease ($R=-0.40$, $p=0.005$), indicating a positive association between better sleep and a healthier diurnal NK cell rhythm.
Conclusion: These results suggest that patients with MBC have reduced NK-cell-mediated immunoprotection compared to controls and that among patients, higher NK cell numbers are related to longer disease-free interval and better Karnofsky status. Patients with MBC also show decreased diurnal NK cell redistribution compared to controls, and among patients, reduced diurnal NK cell redistribution is associated with increased sleep disruption.

Keywords: immune cells; diurnal rhythm; metastatic breast cancer; immunoprotection; sleep

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Circadian profiles of cytokines and HPA axis activity in patients with rheumatoid arthritis: endocrine changes and clinical improvement following treatment with timed-release tablet of prednisone

Background: Joint stiffness in rheumatoid arthritis (RA) is worse in the morning and has been associated with increased secretion of the pro-inflammatory cytokine IL-6 and with decreased secretion of cortisol, suggesting that clinical symptoms may be related to hormonal and immune circadian variations. We measured 24-h blood profiles of IL-6 and cortisol in patients with RA to determine any changes in IL-6 and cortisol following a 2-week course of prednisone administered orally in a specially designed timed-release tablet (TRT).
Methods: Nine patients with active RA were clinically assessed and had 24-h blood sampling before and after a 2-week course of TRT prednisone (5 mg per day). Patients took the TRT orally at 2200 h, and the prednisone was released at 0200 h. Changes in circadian variation in cortisol and IL-6 and clinical measures were compared using random coefficient regression modelling and Wilcoxon matched-pairs signed-rank test.
Results: IL-1ra, IL-1β, IL-4 and TNF showed no circadian variation prior to TRT prednisone. Significant alterations in circadian profiles and concentrations of IL-6 and cortisol were observed following TRT prednisone. The peak value of IL-6 fell from 42.5 to 21.3 pg/ml and occurred earlier (0134 h compared to 0827 h) ($p < 0.005$). Following TRT prednisone, the peak value of cortisol increased from 14.1 to 19.3 μg/dl, and the trough fell from 2.9 to 2.1 μg/dl ($p < 0.001$). There was a close correlation between reduction of IL-6 and improvement in morning joint stiffness following TRT.
Conclusions: These experiments cast new light on circadian patterns of cytokines and hormones in a chronic inflammatory disease. We propose that these changes in IL-6 and cortisol, prior to the onset of morning joint stiffness, are functionally important in mediating the improvement in joint stiffness following prednisone in patients with RA.

Keywords: cytokines; cortisol; IL-6; chronic inflammatory disease; patients; arthritis

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CRH receptor genetic variation in a developmental primate model relevant to the risk to develop anxiety and depression

Background: Using a well-established non-human primate model of anxious temperament (AT) we characterized alterations in the neural circuit that underlie the dispositional risk to develop anxiety and depression. Genetic variation encoding the *CRHR1* and *CRHR2* receptors was determined to examine the extent to which putative functional variants in the expression of these receptors may contribute to the expression of the risk phenotype as well as its underlying neural substrate. In a subset of monkeys, we sampled tissue from the central nucleus of the amygdala (Ce) to quantitate mRNA expression patterns.
Methods: In a large cohort of young rhesus monkeys ($n > 300$), all part of a multigenerational family pedigree, we characterized AT with threat-related behavioral and cortisol measures and its underlying neural circuit with FDG-PET. In all animals, all exons from these genes were sequenced and SNPs with potential functional significance were tested for their relation to AT and brain metabolism in regions underlying AT. Rhesus Affymetrix microarrays were used to determine Ce gene expression patterns.
Results: Regarding *CRHR1*, we found that SNPs affecting exon 6 of *CRHR1* influence both AT and metabolic activity in the anterior hippocampus and Ce. Data will also be presented regarding variation in *CRHR2* in relation to AT, cortisol, and underlying brain function. Gene expression data from the Ce demonstrated alterations in diverse systems, including neuroplasticity.
Conclusions: These data suggest that genetic variation in *CRHR1 and CRHR2* affects the risk for anxiety and affective disorders by influencing the function of the neural circuit underlying AT, and that differences in gene expression or the protein sequence involving *CRHR1* exon 6 may be important. Exon 6 is of particular interest because its expression in primates is very different than that in non-primate species. In addition, Ce mRNA data implicate neuroplasticity systems in the development and maintenance of AT. These data suggest novel treatment

approaches for early life interventions with the potential to decrease the risk of children with AT to develop anxiety and depressive disorders.

Keywords: CRH; primate; anxiety; temperament; SNP; mRNA

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Region-specific alterations in the corticotropin-releasing factor and glucocorticoid receptors in the postmortem brain of suicide victims

Rationale: Abnormalities of hypothalamic–pituitary–adrenal (HPA) axis in depression and suicide are among the most consistent findings in biological psychiatry. However, the specific molecular mechanism associated with HPA axis abnormality in the brain of depressed or suicidal subjects is not clear. It is believed that abnormal HPA axis is caused by increased levels of corticotropin-releasing factor (CRF) and decreased levels of glucocorticoid receptor (GR) in the brain of depressed or suicide subjects. To study their role in teenage suicide, we determined the protein and gene expression of CRF, CRF receptors, and GR in the prefrontal cortex (PFC), hippocampus, and amygdala of teenage suicide victims and teenage normal control subjects.
Methods: The postmortem brain samples were obtained from the Maryland Brain Collection at the Maryland Psychiatric Research Center, Baltimore, MD, USA. Samples were obtained from 24 teenage suicide victims and 24 normal teenage control subjects. Psychological autopsy was performed and the subjects were diagnosed according to the *DSM*-IV (SCID). Protein expression was determined using Western blot and gene expression (mRNA) was determined using real-time RT-polymerase chain reaction (qPCR) technique.
Results: We observed that the protein and gene expression of the CRF was significantly increased in the PFC (Brodmann area 9) and in amygdala, but not in the hippocampus, of teenage suicide victims compared with normal control subjects. The protein and gene expression of CRF-R1 was significantly decreased in the PFC and amygdala, but not in the hippocampus, of suicide victims. We also observed a significant decrease in the protein and mRNA expression of GR in the PFC and amygdala, but not in the hippocampus, of teenage suicide victims compared with control subjects.
Conclusion: These results thus indicate that suicidal behavior is associated with increased CRF and decreased GR in certain specific areas of the brain of suicide victims compared with controls.

Keywords: corticotropin-releasing factor (CRF); glucocorticoid receptor; suicide; depression; CRF-R1

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Genetic variation and HPA axis activity: implications for diagnosis and treatment

Background: Hypothalamic-pituitary-adrenal (HPA) axis activity remains a major focus for the study of the pathophysiology of anxiety and depressive disorders. Recent developments in genetics allow for potential new avenues for assessing risk and for developing new treatments. We will address recent studies on genetics of HPA axis dysregulation in a preclinical model of anxiety/depression, the brains of suicide victims, and severely ill delusional and nondelusional depressives. Last, the development of new glucocorticoid receptor (GR) antagonists that may prove useful as therapeutics in major psychiatric disorders is reviewed.
Methods: Ned Kalin will first present data on a stress model of anxiety/depression in rhesus monkeys. Over 400 monkeys were characterized on behavior and positron emission tomography imaging in response to an intruder and were genotyped for alleles for both corticotropin-releasing hormone receptors (CRH-R1 and CRH-R2). Shyam Pandey will report on gene expression for CRH-R1, CRH-R2, GR, and the mineralocorticoid receptor (MR) in multiple brain regions of adolescents who committed suicide and in matched controls who did not. In a sample

of 122 subjects, Alan Schatzberg will present data on genetic variation differences in GR and CRH-R1 between severely depressed patients (delusional and nondelusional) and healthy controls as well as on the relationship of CRH and GR alleles to mean cortisol activity collected hourly from 6 PM to 1 AM as well as from 1 AM to 9 AM. Finally, Joseph Belanoff of Corcept Therapeutics will discuss the application of medicinal stereochemistry in the development of GR antagonists with greater GR specificity and organ selectivity than those currently available.
Results: Associations between allelic variations in HPA axis genes and behavior were observed for CRH-R1 and CRH-R2 alleles in the rhesus monkey. Decreased message expression for GR and CRH-R1 was observed in key brain regions in suicide victims. Allelic variation for CRH_R1 and GR was associated with risk for severe depression and psychosis, and GR alleles were associated with elevated cortisol levels. A number of nonsteroidal GR antagonists have been synthesized and are active in various animal models.
Conclusions: HPA axis remains a potential source of diagnostic tests and innovative treatment.

Keywords: corticotropin-releasing hormone; glucocorticoid receptor; anxiety; suicide; GR antagonists

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Association of CRHR1 and CRHR2 with major depressive disorder and panic disorder in a Japanese population

Background: Major depressive disorder (MDD) and panic disorder (PD) are common and disabling medical disorders with stress and genetic components. Dysregulation of the stress response of the hypothalamic–pituitary–adrenal axis, including the corticotrophin-releasing hormone (CRH) signaling via primary receptors (CRHR1 and CRHR2), is considered to play a major role for onset and recurrence in MDD and PD.
Methods: To confirm the association of CRHR1 and CRHR2 with MDD and PD, we investigated 12 single nucleotide polymorphisms (SNPs) in MDD patients ($n = 173$), PD patients ($n = 180$) and healthy controls ($n = 285$).
Results: The SNP rs110402 and rs242924 in the CRHR1 gene and the rs3779250 in the CRHR2 gene were associated with MDD. The SNP rs242924 in the CRHR1 gene was also associated with PD. The T-A-T-G-G haplotype consisting of rs7209436 and rs173365 in CRHR1 was positively associated with MDD. The T-A haplotype consisting of rs7209436 and rs110402 in CRHR1 was positively associated with MDD. The C-C haplotype consisting of rs4722999 and rs37790 in CRHR1 was associated with PD.
Conclusion: These results provide support for an association of CRHR1 and CRHR2 with MDD and PD.

Keywords: CRHR1; CRHR2; major depressive disorder; panic disorder; Japanese population

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Development of specific glucocorticoid receptor antagonists

Background/Methods: Mifepristone, a potent glucocorticoid receptor (GR) and progesterone receptor (PR) antagonist, has recently become the first medication approved for the treatment of Cushing's syndrome, the archetypal illness of cortisol excess. Mifepristone is also being studied for the treatment of psychotic depression in a Phase 3 study and in numerous academic studies on diseases in which GR antagonism is thought to be potentially useful. In all cases, mifepristone utility is generated by its ability to block GR and its antagonism of PR is either irrelevant or troublesome. A selective GR antagonist may confer the same benefits of mifepristone while removing an important liability.
Results: Data are provided from animal and human studies of mifepristone and animal studies of novel, selective GR antagonists in metabolic and psychiatric diseases.
Conclusions: Pre-clinical studies indicate that selective GR antagonists may potentially have the same clinical utility as mifepristone in blocking cortisol while eliminating the unwanted effects of progesterone blockade.

Keywords: mifepristone; Cushing syndrome; psychotic depression; cortisol; progesterone blockade

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Role of the endocannabinoid system in extinction of fear memories: lessons from animal studies

Rationale: Generalized avoidance belongs to the core symptoms of a variety of anxiety disorders such as panic disorder or posttraumatic stress disorder. However, therapy for avoidance behavior still bears many obstacles. Even though exposure-based approaches are the method of choice, they suffer from inferior patient compliance. This can be ascribed to patients' inability to stand the high emotional load experienced during the therapeutic sessions. The situation could be much improved if (1) learning about the safety of a feared situation could be enforced, while (2) the negative effect inherent to the exposure is decreased. This would allow for the number/duration of the exposure sessions to be restricted to a minimum, and at the same time, the emotional load of the therapeutic sessions could be dampened, with direct consequences on compliance rates. So far, however, most of the treatments with anxiolytic capabilities (e.g., benzodiazepines) lead to state-dependency or amnesia, with the consequence that safety learning is attenuated, if not completely blocked.
Methods: The role of the endocannabinoid system in fear relief and safety learning was investigated in numerous animal studies employing pharmacological and genetic approaches. Behavioral experiments involved classical fear conditioning and inhibitory avoidance learning, followed by extinction training and safety learning. Mice were treated with the CB1 receptor antagonist/inverse agonist SR141716 (3 mg/kg) or the endocannabinoid uptake/degradation inhibitor AM404 (3 mg/kg). Parts of the experiments were performed with conventional and conditional mice lacking expression of CB1 receptors either in the entire brain or in distinct neuronal populations.
Results: Our studies revealed the following key findings: (1) Endocannabinoids play an essential role in acute fear relief, once the averseness of the test situation exceeded a certain threshold. (2) These effects are mediated via CB1 on glutamatergic nerve terminals. (3) The capacity of the endocannabinoid system is limited in highly aversive situations but can be reestablished by blocking of endocannabinoid uptake/degradation. (4) At the same time, signaling via CB1 on dopamine D1 receptor positive neurons contributes not only to acute fear relief but also to safety learning in an inhibitory avoidance task. (5) The efficiency of safety learning in this task can be improved and the risk of relapse of avoidance behavior can be reduced by pharmacological enhancement of endocannabinoid signaling.
Conclusion: Drugs promoting endocannabinoid signaling via CB1 receptors may represent a new class of compounds that combine the advantages of "happy pills" (in terms of fear and stress relief) with those of "smart drugs" (i.e., facilitated safety learning), thus increasing compliance rates and success of exposure-based therapies in anxiety disorders.

Keywords: endocannabinoid; fear extinction; CB1 receptor; exposure therapy; safety learning

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Bidirectional regulation of endocannabinoid signaling in the amygdala contributes to activation and adaptation of the stress response

Rationale: Endocannabinoids have been shown to be important for the regulation of multiple aspects of the stress response, although the neural circuits underlying this phenomenon are not well characterized. The amygdala is rich in cannabinoid receptors and endocannabinoid content and is well seated to integrate the role of endocannabinoid signaling to the regulation of the stress response. This series of studies sought to determine the roles of the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) in the amygdala with respect to both activation and adaptation of the stress response.
Methods: For the first two experiments, male Sprague-Dawley rats were employed. For acute activation of the stress response, a 30 min exposure to restraint stress was employed, while 9 days of 30 min restraint was employed to

examine adaptation of the stress response. In the third study, C57Bl/6 mice (both wild type and those deficient in the AEA degrading enzyme fatty acid amide hydrolase, FAAH) were employed.
Results: Exposure to acute restraint stress increased the hydrolytic activity of FAAH and decreased AEA content within the amygdala. Local administration of a FAAH inhibitor (10 ng) into the basolateral amygdala (BLA) reduced stress-induced corticosterone secretion, indicating that a FAAH-mediated loss of AEA signaling in the BLA contributes to activation of the stress response. Following 9 days of repeated restraint, the corticosterone response to stress habituated, and this adaptive response was reversed by local administration of AM251 (1 μg), a CB1 receptor antagonist, into the BLA. Consistent with this, repeated restraint stress caused an increase in 2-AG content within the amygdala, indicating that a recruitment of amygdalar 2-AG signaling is required for stress adaptation. Chronic stress exposure caused an increase in FAAH activity and a reduction in AEA content within the amygdala. FAAH deficient mice did not exhibit this reduction in AEA content and were similarly protected against the ability of chronic stress to cause dendritic expansion and spine growth within the BLA, as well as heightened indices of anxiety.
Conclusion: These findings indicate that AEA and 2-AG signaling at the CB1 receptor within the amygdala both serve to inhibit activation of the stress response. AEA appears to serve more of a tonic, gatekeeper role, the loss of which promotes activation of the stress response. Prevention of this loss of AEA signaling, through a blockade of FAAH activity, is capable of dampening the effects of acute and chronic stress. On the other hand, 2-AG signaling is recruited by repeated restraint stress to promote habituation and adaptation of the stress response. As such, a ying-yang model exists within the amygdala with the two endocannabinoid ligands serving different roles to regulate the stress response.

Keywords: Fatty acid amide hydrolase; endocannabinoid; anadamide; 2-arachidonoylglycerol; CB1 receptor

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Critical role of the endocannabinoid system in mediating rapid glucocorticoid effects on memory for emotionally arousing experiences

Rationale: There is extensive evidence that glucocorticoid hormones impair the retrieval of memory of emotionally arousing experiences. Although it is known that glucocorticoid effects on memory retrieval impairment depend on rapid interactions with arousal-induced noradrenergic activity, the neurobiological mechanism underlying this presumably nongenomically mediated glucocorticoid action remains to be elucidated. Here, we show that the hippocampal endocannabinoid system, a rapidly activated retrograde messenger system, is involved in mediating glucocorticoid effects on retrieval of contextual fear memory.
Methods: For all three experiments, male Sprague-Dawley rats were trained on a hippocampus-dependent contextual fear-conditioning (CFC) task and retention was tested 24 h later. All drugs were administered 60 min before retention testing.
Results: Systemic injections of corticosterone (3.0 mg/kg) impaired memory retrieval of CFC training ($P < 0.05$) whereas lower doses (0.3 or 1.0 mg/kg) were ineffective. The retrieval-impairing dose of corticosterone significantly increased hippocampal levels of the endocannabinoid 2-arachidonoylglycerol (2-AG) ($p < 0.05$), but not anandamide, whereas an intra-hippocampal infusion of the cannabinoid receptor type 1 (CB1) antagonist AM251 (0.35 ng) prevented the corticosterone-induced memory retrieval impairment. We further found that an intra-hippocampal infusion of the CB1 receptor agonist WIN55,212-2 (10 ng) impaired memory retrieval of CFC training ($p < 0.001$), and that this impairment was blocked by co-administration of the β-adrenoceptor antagonist propranolol (1.25 μg). In contrast, blockade of hippocampal CB1 transmission with AM251 failed to attenuate memory retrieval impairment induced by concurrent infusions of norepinephrine (1–3 μg).
Conclusion: These findings indicate that glucocorticoid-induced memory retrieval impairment depends on functional interactions between the endocannabinoid and noradrenergic systems.

Keywords: Glucocorticoid; endocannabinoid; anadamide; 2-arachidonoylglycerol; CB1 receptor; memory

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Endocannabinoids in stressed humans

Rationale: The endocannabinoid system has been shown to be an important regulator of the stress response and adaptation to stressful situations and environments in animals. Little is known, however, about the role of this system in acutely and chronically stressed humans.
Methods: We developed an HPLC-MS-MS-based method to measure plasma concentrations of the ECs anandamide (ANA), 2-arachidonoylglycerol (2-AG), the N-acyl-ethanolamides palmitoylethanolamide (PEA), oleoylethanolamide (OEA), stearoylethanolamine (SEA), and N-oleoyldopamine (OLDA), determined leucocyte cannabinoid (CB) receptor mRNA and genotyped the CB receptor genes (CB1/CB2) for known single nucleotide polymorphisms in critically ill patients.
Results: We used these methods in a number of studies in healthy volunteers, critically ill patients, and individuals with PTSD to delineate the relationship between peripheral EC signaling and the intensity of acute and chronic traumatic stress. In a first series of experiments, we exposed healthy volunteers ($n = 21$) to acute kinetic stress during a parabolic flight experiment. Stress-tolerant participants ($n = 14$) showed a significant increase in plasma EC concentrations and unchanged plasma cortisol concentrations whereas highly stressed individuals ($n = 7$) showed an absent EC response, a reduced expression of leukocyte CB1 mRNA, and a massive activation of the hypothalamic-pituitary-adrenal axis. Physical stress in trained and physically fit individuals ($n = 12$) induced by hard exercise during mountaineering or cycling also resulted in elevated EC concentrations, which returned to baseline after termination of the stressful activity. In contrast, chronically stressed individuals with traumatic memories from war and torture experiences with ($n = 10$) and without PTSD ($n = 18$) showed persistent elevations of plasma EC concentrations when compared to non-traumatized controls ($n = 20$). EC plasma levels correlated with scores on the clinician-administered PTSD scale. Analogous findings came from an earlier study in patients with heart disease awaiting cardiac surgery ($n = 90$). In this study, patients with traumatic memories and evidence of PTSD from previous life-threatening experiences associated with cardiac disease ($n = 57$) and evidence of PTSD ($n = 8$) had significantly higher EC plasma concentrations than patients without traumatic memories and PTSD symptoms. Furthermore, a very recent study in patients after cardiac surgery ($n = 95$) found an association between a single nucleotide polymorphisms of the gene encoding the CB2 receptor and the intensity of post-traumatic stress symptoms after surgery.
Conclusion: These findings point to a possible involvement of the EC system in acutely and chronically stressed humans with traumatic memories and PTSD. Additional studies of EC signaling in PTSD patients before and after therapeutic interventions could lead to novel biomarkers and to further progress in the understanding of PTSD and the multiple biological and behavioral sequelae of this complex disorder.

Keywords: PTSD; endocannabinoid; anadamide; 2-arachidonoylglycerol; CB1 receptor; CB2 receptor

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Positron emission tomography offers new perspectives for evidence-based treatment development in PTSD

Background: Combat-related posttraumatic stress disorder (PTSD) is increasingly recognized as a primary challenge to the fitness of American military personnel and represents a significant military and national public health concern (Hoge et al. 2004; Thomas et al. 2010). A few available drugs (e.g., selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors) provide some benefit in the management of PTSD symptoms and have been approved by the Food and Drug Administration for the treatment of PTSD, but most meta-analytic reviews (Stein et al., 2006) have concluded that the benefits are minimal and there may be relatively less benefit for combat veterans (Friedman et al., 2007). Popular augmentation strategies using second-generation antipsychotic medication were also recently shown to be ineffective in the treatment PTSD (Krystal et al., 2011). Deficits in CB_1 receptor–mediated eCB signaling may play a key role in the etiology of PTSD and may mediate important components of the PTSD phenotype. Therefore, we propose to enhance eCB signaling as a novel, evidence-based treatment for PTSD with the potential to prevent both the behavioral (anxiety, impaired extinction) and molecular adaptations to trauma (increased CB_1 receptor expression; Suarez et al., 2009) associated with PTSD.

Methods: Using radioligands and positron emission tomography (PET) imaging on a high-resolution PET scanner, we tested novel models of the etiology of PTSD involving these systems and their associated receptors.
Results: Four main lines of translational evidence implicate a defect in CB_1 receptor–mediated eCB signaling in the pathogenesis of PTSD. In initial experiments, we found that (*a*) plasma AEA levels are decreased in PTSD patients (0.72 ± 0.12 pmol/ml) relative to healthy control subjects without trauma history (HC 2.74 ± 0.85 pmol/ml, $t = 2.47$, $df = 17$, $p = .024$) or controls with trauma history (TC 2.67 ± 0.36, $t = 2.81$, $df = 10$, $p = 0.018$); (*b*) there are statistically detectable correlations between earlier age at first trauma and lower AEA levels in PTSD ($r = 0.45$, $p = 0.073$) and between magnitude of the decrease with a longer duration of PTSD ($r = -0.48$, $p = 0.059$); (*c*) there are elevated [^{11}C]OMAR volume of distribution (V_T) levels (corresponding to elevated CB_1 receptor density) in the fear circuit in PTSD relative to healthy people. This upregulation develops to compensate for the existing eCB deficit in PTSD and causes impaired fear processing, increased stress sensitivity and anxiety in PTSD as supported by (*d*) a statistically detectable positive correlation between amygdala [^{11}C]OMAR V_T and anxiety symptoms ($r = 0.56$, $p = 0.09$), perceived stress ($r = 0.57$, $p = 0.018$), and abnormal fear processing measured during fear conditioning tests ($r = 0.69$, $p = 0.003$).
Conclusions: These first data in PTSD provide evidence for abnormal CB1 receptor–mediated endocannabinoid signaling in PTSD and also provide a basis for evidence-based treatment development for this patient population. Inhibition of fatty acid amid hydrolase, the endocannabinoid degrading enzyme, appears to be an attractive candidate for such an undertaking.

Keywords: PTSD; endocannabinoids; CB1 receptor; brain imaging; positron emission tomography; novel treatments

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Animal model of PTSD based on clinically relevant features of trauma susceptibility and expression

Rationale/statement of the problem: There is an insufficient understanding of the neurobiology of post-traumatic stress disorder (PTSD). Therefore, the development of an animal model of PTSD that takes into account clinical features of the disorder is of value toward enhancing our understanding of the mechanisms, and in the development of novel treatments, of emotional trauma.
Methods: Adult male rats were administered chronic psychosocial stress composed of two 1-hour periods of inescapable exposure to a cat, in conjunction with daily unstable pair housing, over a 31 day period. The rats were then given a battery of tests, including measures of behavior (anxiety testing, startle response), cognition (predator-based fear memory and new memory testing), hormone levels (basal and evoked glucocorticoids), responses to pharmacological agents (dexamethasone and yohimbine) and cardiovascular activity (blood pressure/heart rate). In addition, we measured epigenetic alterations (methylation) of the brain-derived neurotrophic factor (BDNF) gene.
Results: Psychosocially stressed rats exhibited a PTSD-like phenotype. The stressed rats exhibited a strong fear-conditioned memory of the two cat exposures, an increase in behavioral signs of anxiety, an exaggerated startle response, increased blood pressure, greater sensitivity to yohimbine and a hippocampus-dependent memory impairment, relative to controls. In addition, stressed rats exhibited reduced basal glucocorticoid levels, greater sensitivity to dexamethasone and hypermethylation of the BDNF gene in the hippocampus.
Conclusion: These findings demonstrate that intense psychosocial stress produced dramatic changes in physiology and behavior in rats which are comparable to those observed in people diagnosed with PTSD. This rat model, therefore, may enhance our understanding of the mechanisms underlying human trauma and in the development of more effective pharmacotherapy for people with PTSD.

Keywords: PTSD; animal model; trauma susceptibility; gene expression; cognition; hormone levels

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Contextual processing deficits in PTSD: from animal models to fMRI studies

Background: Context processing imbues appropriate salience to the stimuli that is encountered. This ability enables us to hide from a predator in the wild, but to enjoy a visit to the zoo, although the lion may look the same in both contexts. Failures in contextual processing can lead to inappropriate fear responses rooted in failures to use safety cues, consider internal states, anticipate events, or appraise them properly. Posttraumatic stress disorder (PTSD) is associated with exaggerated fear, unwanted recollection, and inappropriate emotional and social responses. We proposed that PTSD pathophysiology involves deficits in context processing and examined this hypothesis using PTSD animal model and fMRI studies in patients with PTSD.
Methods: Using validated animal model of PTSD, we examined fear conditioning, fear extinction and context-dependent extinction recall, and fear renewal in single prolonged stress (SPS)-exposed animals. We further examined the relationships between glucocorticoid receptors (GRs) upregulation in SPS, and fear renewal deficits were observed. Using 3T fMRI paradigm, we examined fear conditioning, fear extinction, extinction recall, and fear reinstatement in PTSD patients and trauma-exposed control subjects.
Results: In humans, we found that fear-conditioning procedures activated fear-associated brain regions, but PTSD patients had similar fMRI activation maps to trauma-exposed controls during fear conditioning and extinction. However, they exhibited decreased responses to contextual signals of safety and danger. In animal work, we found that the SPS-exposed animals exhibited normal levels of conditioning and extinction, but specific deficits in context-dependent extinction recall and fear renewal. In ''dismantling'' studies, only animals exposed to full SPS and that demonstrated largest upregulation of GR in hippocampus and prefrontal cortex exhibited fear renewal deficits.
Conclusions: hese results demonstrate contextualization deficits in PTSD subjects. PTSD animal model findings mirror those observed in PTSD patients and further implicate specific molecular targets in defined brain regions in contextualization deficits. Together, this set of studies demonstrates the combined power of translational research into trauma psychopathology.

Keywords: PTSD; context processing; fear responses; fMRI; hippocampus; prefrontal cortex

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Toward reconsolidation blockade as a novel treatment for PTSD

Rationale/statement of the problem: Animal research has challenged the permanency of memory by suggesting that reactivation (retrieval) of a specific memory may return it to a labile state from which it must be ''re-consolidated'' if it is to persist. Pharmacologically blocking reconsolidation offers the therapeutic possibility of weakening traumatic memories in post-traumatic stress disorder (PTSD).
Methods: We have been testing the above hypothesis using systemic drugs approved for human use. In rats we employ classical conditioning consisting of pairing a tone CS with a shock US on Day 1 (acquisition), presenting the tone without shock on Day 2 (reactivation) followed by drug, and then re-presenting the CS alone on Days 3 and 10 (tests). We have also used slice electrophysiology to measure the increase in cortico- and thalamo-lateral amygdala synaptic efficacy as a result of the tone-shock association, and then decrement in this efficacy following reconsolidation blockade. In PTSD subjects, we have administered oral drug along with verbal or written narration of the traumatic event (reactivation) and subsequently measured the strength of the traumatic memory via psychophysiological recording during script-driven imagery, and/or symptom report.
Results: In animal work, we have found that the antiglucocorticoid receptor mifepristone, the protein synthesis inhibitor rapamycin, and the alpha-2-adrenergic autoreceptor agonist clonidine all block partially reconsolidation of conditioned fear. Clonidine does so in a dose-dependent manner. Additionally, rapamycin reverses the synaptic enhancement described above, providing an underlying physiological basis for reconsolidation blockade. In humans, we have found that traumatic memory reactivation plus double-blind, placebo-controlled propranolol

reduce physiologic responding during script-driven imagery, and that six weekly open-label propranolol plus memory reactivation sessions reduce PTSD symptoms to a similar degree as current cognitive behavioral treatments. A double-blind clinical trial is underway.
Conclusion: The above results show progress toward a clinical application of reconsolidation blockade, but much more needs to be done before efficacy is demonstrated.

Keywords: PTSD; mice; classical conditioning; reconsolidation blockade; systemic drugs

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Brain and blood gene expression pathways associated with susceptibility to PTSD

Background: The identification of molecular post-traumatic stress disorder (PTSD) susceptibility pathways associated with different patterns of behavioral response to trauma is essential to an understanding of the neurobiology of PTSD and can pave the design for new treatments. Although several genes have been reported to be differentially expressed in PTSD, methodological constraints have limited the interpretation, for example, variation in the type or magnitude of trauma exposure, inter-individual genetic variation, and tissue specificity of response. Animal models are useful in delineating some of these issues. In this study, we used a unique animal model of PTSD with ecological and population validity. Adult rats were exposed briefly to predator scent stress, which mimics a threatening situation. Rats respond heterogeneously to this type of traumatic stress behaviorally and physiologically, similar to human response variability. In this model, two behavioral extremes can be studied – vulnerable and resistant 'subtypes'.
Methods: Sprague-Dawley rats were exposed to the scent of cat urine. The outcome measures included behavior in an elevated plus-maze and the acoustic startle response 7 days after exposure. Cut-off behavioral criteria classified exposed rats according to their behavioral response as those with 'extreme behavioral response' and 'minimal behavioral response' (MBR), with unexposed rats as controls. From the tissue obtained 24 h after the behavioral tests, basal gene expression using Illumina BeadArrays was evaluated for whole blood and three brain areas: amygdala, anterior cortex and hippocampus. For data quality control and differential expression analysis, we used R and LIMMA (as included in MeV software), respectively. Pathway analysis was performed with ingenuity.
Results: There was only minimal overlap in gene expression across brain regions and gender demonstrating the existence of distinct tissue-specific susceptibility pathways in male and female rats. Among the differentially expressed genes, the ones regulated by the glucocorticoid receptor (e.g., FKBP5, Per-1, and NPY) were particularly over-represented (especially in blood and hippocampus), indicating that glucocorticoid regulation is involved in vulnerability and resistance to trauma. The observed gene expression profiles may also indicate the over-representation of discrete functional biological clusters and pathways (e.g., MAPK signaling and circadian rhythm).
Conclusions: Glucocorticoid-related gene expression is underlying the different response pattern following trauma, with distinct regional/structural differences between male and female rats.

Keywords: PTSD; gene expression; susceptibility; glucocorticoid regulation; neurobiology; glucocorticoid receptor

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A novel mouse genetic model for post-traumatic stress disorder

Rationale/statement of the problem: Post-traumatic stress disorder (PTSD) arises from the interaction of genetic and environmental factors. Thus, a better understanding of the molecular etiology of PTSD would

be greatly facilitated by the development of animal models that explore gene × environment interaction in the context of traumatic stress. To this end, we have identified a new mouse genetic model for stress vulnerability that may provide novel insight into the neurobiology of PTSD. Our studies focus on mice that are deficient for TIA-1, a prion-related RNA binding protein that regulates the expression of multiple target genes in the mammalian brain.

Methods: TIA-1 KO mice and wild-type littermates are generated from TIA-1 heterozygous crosses. All behavioral (fear conditioning, open field, elevated-plus maze, forced-swim test) and electrophysiological (hippocampal field recordings) experiments are conducted in accordance with standard protocols.

Results: Under baseline conditions, TIA-1 KO mice are indistinguishable from wild-type controls in all behavioral and neuroendocrinological measures evaluated thus far. However, several weeks after exposure to contextual fear conditioning, TIA-1 KO mice demonstrate increased anxiety and despair-like behavior, as well as abnormal glucocorticoid production. Moreover, these phenotypes are observed predominantly in female animals. Electrophysiological studies reveal aberrant synaptic plasticity in the ventral hippocampus of knockout animals in response to corticosterone treatment, consistent with a critical role for TIA-1 in normal emotional memory formation in the hippocampus during stress. Finally, molecular data suggest that TIA-1 may regulate alternative splicing of the glucocorticoid receptor, which is known to be important for both hypothalamic-pituitary-adrenal (HPA) axis function and hippocampal synaptic plasticity during stress.

Conclusion: TIA-1 KO mice recapitulate several key features of chronic PTSD observed in humans. Thus, our studies demonstrate that TIA-1-deficient mice represent a useful model in the study of gene × environment interaction during traumatic stress, and may contribute to our knowledge of the molecular basis of PTSD. Finally, because individuals with PTSD are also susceptible to substance abuse, we, therefore, discuss the utility of TIA-1 knockout mice in the study of PTSD and comorbid substance use disorders.

Keywords: genetic model; PTSD; mice; substance use; anxiety

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Affective style and early life experiences moderate cortisol's effects on emotional learning

Background: Relatively little is known about how lasting qualities of the individual (e.g., traits and/or one's past history) moderate the effects of cortisol on emotional learning. We hypothesized that cortisol would have more pronounced effects on memory formation in individuals who show greater levels of trait negative affect (Trait NA) or who experienced early life separation (ELS).

Methods: In Study 1, involving 42 healthy adults (22 women), we examined how Trait NA moderated the effects of cortisol administration (IV-administered 0.1 mg/kg/30 min hydrocortisone; CORT) vs. placebo on memory formation for unpleasant and neutral photographs. In a preliminary study (Study 2), in 18 depressed adults (10 women), we examined how ELS (because of parental divorce or permanent separation) moderated the effects of CORT (15 mg orally administered hydrocortisone) vs. placebo on memory formation for positive and negative words.

Results: In Study 1, we found that in women with higher Trait NA, CORT facilitated memory formation. In women with lower levels of Trait NA, CORT had no effects of memory formation. Study 2 revealed that in depressed women with ELS, CORT facilitated memory formation for negative words. Specifically, CORT (vs. placebo) biased memory in a negative direction by an average of 4.2 (SD = 0.73) words in women with ELS. In depressed women without ELS, CORT had no effect on memory formation. In both studies, 1 & 2, effects were less robust in men or trended in the opposite direction, which may represent true sex differences or may be because of confounding factors, such as differences in cortisol elevations for men vs. women.

Conclusions: In summary, our data suggest that lasting qualities of individuals, such as Trait NA or history of early separation, moderate cortisol's effects on emotional memory. Further investigation into how variation in personal traits and past experiences moderate cortisol's effects on emotional cognition is one important step in elucidating why some individuals are more sensitive than others to the detrimental (e.g., negatively biasing) effects of stress on emotional cognition and memory. These data may also inform research regarding the use of corticosteroid receptor

ligands in treatment for psychopathology. Individual differences in affective style or past experiences may predict therapeutic response to corticosteroid receptor ligands.

Keywords: emotional memory; learning; cortisol; early life separation; trait negative affect

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Stress, genes and emotional memory: implications for anxiety disorders

Background: Enhanced memory for emotional events is a well-known phenomenon. From an evolutionary perspective, it is an adaptive mechanism, as it helps to remember threatening as well as pleasurable experiences. Stress hormones are important players in the regulation of emotional memory. Specifically, in animals and in humans, glucocorticoids enhance memory consolidation of emotionally arousing experiences but impair memory retrieval. Glucocorticoid actions are partly mediated by glucocorticoid receptors in the hippocampus, amygdala and prefrontal cortex, key brain regions for emotional memory. Here, we investigated whether the BclI polymorphism of the glucocorticoid receptor gene is associated with emotional memory in healthy young subjects. This polymorphism has been previously related to traumatic memories and posttraumatic stress disorder (PTSD) symptoms in patients who underwent heart surgery (Hauer et al., 2011).
Methods: To assess memory performance, we used a picture-learning task consisting of learning and recalling emotional and neutral photographs on two consecutive days in 841 healthy young subjects. Genotyping of the BclI polymorphism was done with Pyrosequencing on a PyroMark ID System.
Results: The BclI variant was associated with short-delay recall of emotional pictures: GG-carriers showed increased emotional memory performance as compared to CG- and CC-carriers. We did not find a genotype-dependent difference in recall performance for neutral pictures.
Conclusion: These findings indicate that the BclI polymorphism contributes to inter-individual differences in emotional memory in healthy young subjects and suggest a genetic link between emotional memory in healthy humans and traumatic memory in patients who underwent cardiac surgery.

Keywords: BclI; memory; emotion

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Time-dependent effects of cortisol on the contextual dependency of negative and neutral memories

Background: The inability to store fearful memories into their original encoding context may be an important vulnerability factor for developing anxiety disorders like posttraumatic stress disorder (PTSD). Such altered memory *contextualization* may develop through the effects of the well-known stress hormone cortisol on underlying memory neurocircuitry, rich in corticosteroid receptors. By binding to these receptors, cortisol induces rapid non-genomic effects followed by slower genomic effects that are thought to modulate cognitive function in various ways. Here, we tested these time-dependent effects of cortisol on the contextualization of negative versus neutral memories.
Methods: In a double blind, placebo-controlled design, 60 men were randomly assigned to one out of three possible groups. 1) In the rapid cortisol group, participants received 10mg hydrocortisone 30 min before completing the "associative imagination task" (AIT), 2) while the slow cortisol group received the drug 240 min before the task. 3) A third group received placebo at both times. During the AIT task, participants were instructed to vividly imagine 30 neutral and 30 negative words in unique background pictures. Approximately, 24 h later, participants completed

two surprise memory tests: cued retrieval and recognition. Crucially, to assess memory contextualization, half of the negative and neutral words were tested in intact contexts, whereas the other half of the words were tested in rearranged context combinations.
Results: Recognition data showed that negative memories were generally less context-bound than neutral memories. Moreover, cortisol exerted time-dependent effects on contextual dependency of *negative* memories: Cortisol' rapid effects impaired contextualization, whereas cortisols' slow effects enhanced negative memory contextualization. In contrast, neutral memory contextualization remained unaltered by cortisol irrespective of the timing of the drug.
Conclusions: This study shows distinct time-dependent effects of cortisol on the contextualization of negative memories. These results suggest that non-genomic effects of cortisol may underlie impaired memory contextualization observed in PTSD, whereas genomic effects of cortisol may open avenues for cortisol as a protective agent against (traumatic) fear memory generalization.

Keywords: cortisol; PTSD; memory; cognitive testing

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Cortisol facilitates memory by enhancing hippocampal activation and functional connectivity

Background: Stress and stress hormones (e.g., cortisol) modulate memory processes in both facilitative and deleterious ways, but mechanisms of memory enhancement are not yet fully understood. Specific effects of cortisol may be of particular interest, given its importance in a range of stress-related illness that is associated with cognitive changes.
Methods: To elucidate potential mechanisms of memory facilitation via pharmacological manipulation; healthy participants underwent functional magnetic resonance imaging after oral-administration of 100 mg of hydrocortisone ($N = 14$) or placebo ($N = 12$). Participants viewed compound pictures consisting of faces superimposed upon buildings. A surprise memory test was administered 24 h later.
Results: Cortisol at encoding enhanced subsequent memory only for face-building combinations but not for faces or buildings alone. Cortisol increased anterior hippocampal activation and a mediation analysis suggests that cortisol enhancement of conjunctive memory was at least partially mediated through this enhanced hippocampal activity. Cortisol memory enhancement was also associated with increased hippocampal interconnectivity.
Conclusions: These results support the hypothesis that the hippocampus may be an integral participant in cortisol's memory facilitation effects, with potential implications for psychopathologies like posttraumatic stress disorder, that involve stress-axis, hippocampal, and memory abnormalities.

Keywords: stress; genes; glucocorticoids; anxiety disorders

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Modulation of emotional memories upon reactivation: the role of stress hormones

Background: The stress hormone cortisol is known to modulate different memory processes. In general, high levels of cortisol increase memory consolidation, especially for emotional material. For a long time, memories were thought to be stable and resistant to changes after their consolidation was completed. However, recent evidence suggests that consolidated memories are subject to modulation upon their recall (reactivation). This suggests that memory reactivation opens a window of opportunity allowing the memory trace to be modulated in a lasting

manner. Given that cortisol is an important modulator of memory, we were interested in investigating how it could modulate reactivated memories.
Methods: In the first study, 32 healthy men and women encoded a slideshow containing neutral and negative segments. Two days later, all participants recalled the slideshow (reactivation) and were randomly assigned to a stressor, the Trier Social Stress Test (TSST) or a control condition. Memory was reassessed immediately after that, as well as 5 days later. For the second study, 33 healthy men were exposed to the slideshow (as described above). Three days later, they were either administered with a placebo or metyrapone (a cortisol synthesis inhibitor). All participants had to recall the slideshow when the medication was active, and 4 days later. The third study assessed the impact of real negative news from the media. Fifty-six healthy men and women who were media consumers were either exposed to real negative news or to real neutral ones. Subsequently, they were all exposed to the TSST and their memory for the news was assessed 24h later.
Results: Study 1 demonstrated that emotional memory was enhanced following stress and this effect was still observed 5 days later. Study 2 results showed that memory reactivation of the emotional material was lower in the metyrapone group and this deficit was still present 4 days later. Study 3 demonstrated that women who were exposed to real negative news remembered this news more and were more stress reactive to a subsequent stressor.
Conclusions: Memory is an active process that can be updated upon its reactivation and cortisol can act as a modulator of this process. Results of our studies will be discussed with regards to their relevance to the clinical domain, more particularly for posttraumatic stress disorder.

Keywords: glucocorticoids; TSST; emotional memories

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Role of cortisol, sleep, and glucocorticoid receptors in memory consolidation and retrieval

Background: Memory functions involve three stages: encoding, consolidation, and retrieval. Modulating effects of glucocorticoids (GCs) have been consistently observed for encoding and retrieval. However, little is known on how GCs affect consolidation.
Methods: In Study I, after encoding emotional and neutral texts, cortisol or placebo was intravenously infused while participants were either awake ($N=16$) or napped ($N=16$). Study II and III investigate the mechanisms underlying the fact that memory retrieval is impaired at very low as well as very high cortisol levels but not at intermediate levels. Using specific receptor antagonists, we examined the role of mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) in memory retrieval. Using a double-blind within-subject, cross-over design, participants retrieved emotional and neutral material (learnt 3 days earlier) between 7:45 a.m. and 9:15 a.m. after administration of 400 mg of the MR blocker spironolactone vs. placebo (200 mg at 22:30 p.m. and 200mg at 4 a.m., Study II) or the GR blocker mifepristone vs. placebo (200 mg at 23:00 p.m., Study III).
Results: In Study I, retention of temporal order within the texts was enhanced when cortisol was infused during the wake phase but impaired when it was infused during sleep. In Study II, blockade of MRs impaired free recall of both texts and pictures, especially for emotional material. In contrast, blockade of GRs resulted in better memory retrieval.
Conclusions: Study I points toward fundamentally different mechanisms of cortisol on hippocampal memory consolidation, depending on the brain state. Study II and III indicate opposing roles of MRs and GRs in memory retrieval.

Keywords: cortisol; sleep; glucocorticoid receptors; memory consolidation; retrieval

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Early life stress concept: introduction

Rationale/statement of the problem: Stressful experiences during early life can remodel brain circuitry underlying behavioral adaptation with consequences for resilience and vulnerability to emotional and cognitive disorders. At least in the rodent this apparent permanent outcome of early adversity can be modulated by maternal influences and depends on the later life environmental context with the stress hormones of the hypothalamus-pituitary-adrenal axis in the driver's seat. A frequently investigated model is the animal that has experienced as pup reduced maternal care. Such a period of early neglect enhances the pup's responsivity to adverse emotional experiences, an effect that can even be detected within families and was found to advance prematurely the development of emotional and fear circuitry. Alternatively, enhanced care is capable of overridingthe lasting impact of neurotoxicity in early life. For instance, the frequently reported adverse effect of early life treatment with dexamethasone (as life-saving treatment of prematurely born infants) is strikingly attenuated by enhanced maternal care induced by daily handling.
Methods: Dr. Nederhof will review recent animal and human studies supporting the cumulative stress and mismatch hypotheses. Dr. Parker will present behavioral and neuroendocrine data from monkey studies supporting the idea of stress inoculation following early exposure to moderate stressors. Dr. Bagot will address the importance of later-life context when investigating the effects of early-life experience using rats exposed as pups to varying levels of maternal care and ex-vivo electrophysiology. Dr. Vinkers will demonstrate in healthy volunteers a modulation by genotype and gender of the accumulating effects of stress on psychiatric outcome.

Keywords: early life stress; behavioral adaptation; resilience; cognitive disorder; maternal care; signaling pathways

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Mismatch or cumulative stress: two causal mechanisms of psychiatric disease

Rationale/statement of the problem: The cumulative stress hypothesis states that aversive experiences early in life predispose individuals to be more vulnerable to aversive challenges later in life. Indeed, adversity has consistently been associated with psychopathology; however, it is neither a determinative nor a sufficient explanation. The mismatch hypothesis provides an alternative explanation; adverse experiences early in life trigger adaptive processes, thereby rendering an individual to be better adapted to adversity later in life.
Methods: A review of both the animal and human literature on the interaction between early and later adversity and its relation with psychopathology.
Results: In the animal literature, support for both the cumulative stress hypothesis and the mismatch hypothesis was found. The human literature is characterized by a general paucity of interaction studies. Convincing evidence for individual differences in sensitivity to early programming suggests that both hypotheses might be true but applicable to different individuals.
Conclusion: The cumulative stress hypothesis is proposed to apply to individuals who were not or only to a small extent programmed by their early environment, the mismatch hypothesis to individuals who experienced strong programming effects.

Keywords: cumulative stress; mismatch hypothesis; early programming; early adversity

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Early life stress inoculation in monkeys: a pathway to resilience

Early exposure to severe stress in childhood increases the incidence of mood and anxiety disorders in adulthood. Far less researched, but of equal importance, is the theory that moderate early stress exposure instead of increasing vulnerability results in subsequent resilience. Variously described as inoculating, immunizing, steeling, or toughening, the notion that moderate postnatal stress exposure strengthens resistance to subsequent stressors has far-reaching implications for understanding the pathogenesis and prevention of stress-related affective disorders.

Although the psychobiology of stress-inoculation-induced resilience in humans is largely unknown, new insights have emerged from seven studies of monkeys previously exposed to moderate postnatal stress compared to no-stress control-rearing conditions. Evidence from these studies indicates that early exposure to moderate stressors that temporarily stimulate anxiety and activate the hypothalamic-pituitary-adrenal (HPA) axis leads subsequently to diminished negative arousal, prosocial tendencies, enhanced cognitive control, increased curiosity, larger prefrontal cortical volumes, and attenuated HPA axis activation. In contrast to rodents, rearing differences in the development of neuroendocrine stress resistance in monkeys are more closely related to differences in prior stress exposure than to differences in maternal care. In addition, unlike in rodents, no rearing differences in glucocorticoid feedback sensitivity were observed in monkeys, suggesting that the neural basis of stress resistance in primates may differ from that in rodents. Finally, results from a pharmacological study, which further support the key role of acute early anxiety exposure in promoting the development of subsequent behavioral indications of resilience, will be presented. Findings from these non-human primate studies support the intriguing hypothesis that moderate early stress exposure may likewise provide a pathway to resilience in humans.

Keywords: stress inoculation; monkeys; childhood stress; resilience

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Natural variations in maternal care determine sensitivity to glucocorticoid regulation of hippocampal synaptic plasticity and function in adult rats

Rationale: Variations in maternal care in the rat associate with robust differences in hippocampal synaptic plasticity and learning in the offspring. In addition, differences in stress reactivity associate with variations in maternal care. However, the potential influence of stress on hippocampal function is often overlooked in studies of effects of early life experience. Previously, we found differential modulation of hippocampal function and plasticity by stress in adult offspring exposed to varying levels of maternal care. N-methyl-D-aspartate receptors (NMDAR) regulate synaptic plasticity, and NMDAR function is modulated by stress and CORT. We hypothesised that altered NMDAR function underlies the interaction of maternal and stress effects on hippocampal synaptic plasticity.
Methods: We used electrophysiology to examine NMDAR-dependent LTP and NMDAR synaptic function in adult offspring of mothers that varied in the frequency of pup licking/grooming (LG), i.e., High or Low LG.
Results: Under basal conditions, long-term potentiation (LTP) was impaired in the hippocampal dentate gyrus of Low LG offspring relative to High LG offspring. Synaptic NMDAR function was enhanced in Low LG offspring with no change in α-amino-3-hydroxy-methyl-4-isoxazole propionic acid receptor function (AMPAR). NMDAR antagonism by low concentration APV rescued the basal LTP deficit in Low LG offspring and inhibited LTP in High LG offspring. Stress-level CORT (100nM) rapidly enhanced LTP in offspring of Low LG rats and impaired LTP in offspring of High LG rats. CORT robustly increased NMDAR function in High LG offspring, eliminating the maternal effect. CORT did not affect NMDAR function in Low LG offspring. Thus, Low LG offspring exhibit basally elevated NMDAR function coupled with insensitivity to CORT modulation indicative of a chronic alteration of NMDAR.
Conclusion: These results suggest that low maternal care exerts a lasting effect on hippocampal plasticity through enhanced function of NMDAR in synapses. The blunted effect of CORT on synaptic NMDAR in Low LG rats could be adaptive in promoting cognitive functioning in challenging conditions, such as the improved contextual fear conditioning previously observed in these rats.

Keywords: maternal care; glucocorticoid regulation synaptic plasticity

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The effect of cumulative stress exposure on depressive symptoms is modified by a mineralocorticoid receptor haplotype

Rationale/statement of the problem: Stress exposure increases the risk for the development of depression. The leading hypothesis is that stress exposure only increases the risk in individuals combining a vulnerable genetic background with (repeated) stress exposure. However, it is currently unknown which (combination) of stressful life events are the most etiologically relevant to predict depressive symptoms. Preliminary evidence suggests that repeated cumulative stress may have the highest impact.
Methods: We aimed to determine the effects of repeated stress exposure on depressive symptoms (Beck Depression Inventory) in a cross-sectional sample of healthy subjects ($n = 563$). Repeated stress exposure was operationalized as exposure to three stressors: early life stress (Childhood Trauma Questionnaire), later life stress (Life Stressor Checklist) and daily hassles. Because of the importance of the mineralocorticoid receptor (MR) for HPA axis responsivity, we investigated whether the MR haplotype (rs5522 and rs2070951) modified stress-induced depressive symptoms. For genetic analyses, we divided subjects into a low stress exposure group (0–1 positive stress domains) and high stress exposure group (2–3 positive three stress domains). Gender and cannabis use were included as covariates.
Results: Childhood trauma, later life stressors, and current daily hassles independently and cumulatively contributed to depressive symptoms (continuous and dichotomized). High cumulative stress exposure was associated with depressive symptoms ($p = 5.4\text{xe} -20$). This effect was moderated by the MR haplotype ($p = 0.009$) and was more pronounced in female subjects ($p = 3.0\text{xe} -6$).
Conclusion: Cumulative exposure to three independent stressors contributed to the development of depressive symptoms in a healthy sample. Thus, our data implicate the existence of a multiple hit model in which independent but cumulative stress exposure leads to increased depressive symptoms. Multiple assessments across various stress domains may increase the validity and reliability of stress exposure compared to a single assessment. Importantly, the MR haplotype moderated the cumulative effects of stress on depressive symptoms, confirming and extending earlier studies, which showed that the MR haplotype 2 is associated with reduced optimism and a blunted stress response.

Keywords: HPA axis; mineralocorticoid; depressive; gene environment interaction; cumulative stress exposure

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A heartfelt response: oxytocin effects on response to social stress in men and women

Rationale/statement of the problem: Animal research has indicated that oxytocin is involved in social bonding, stress regulation, and positive physiologic adaptations that may be linked with greater longevity and successful aging. Because of its potential role in promoting positive human social behavior, recent research has focused on whether oxytocin may lead to improved social and emotional functioning for various mental disorders. Moreover, given its apparent anti-stress effects, some investigators have posited that oxytocin may provide the basis for the observed beneficial effects of positive social relationships on health. While knowledge of the effects of oxytocin in healthy humans remains limited, the emerging research has raised some doubt as to whether effects are uniformly prosocial or stress-reducing. Moreover, gender differences in these stress-related effects have been speculated but not tested in humans. In this study, we examine whether oxytocin enhances salutary responses to social stress and compare effects between men and women.
Methods: Hypotheses were tested with a placebo-controlled, double-blind experiment, using a between subjects 2 (male vs. female) $\times 2$ (oxytocin vs. placebo) design. Participants ($n = 99$) were randomized to receive either intranasal oxytocin spray or placebo (saline) nasal spray. Social stress was induced using the Trier Social Stress Test (TSST). Baseline measures of estradiol were obtained via saliva samples. Primary outcomes were cardiovascular

(CV) reactivity, objective behavior during the stress task coded by observers unaware of the oxytocin condition, and self-reported affective responses.
Results: Analyses were conducted using two-way analysis of variance models (or ANCOVA if covariates such as age or estradiol were included). Participants given oxytocin, relative to placebo, responded to social stress with a *challenge* orientation characterized by a benign pattern of cardiovascular reactivity. For example, participants given oxytocin, compared to placebo participants, exhibited a trend toward greater increases in cardiac output [$F(1, 68) = 3.31$, $p = 0.07$, $d = 0.47$] and ventricular contractility [indicating more sympathetic activation; $F(1, 71) = 2.98$, $p = 0.09$, $d = 0.45$]. Gender differences also emerged. Men given oxytocin reported less negative affect (e.g., mean change between baseline and social stress task, men = 0.26 vs. women = 2.14) and had greater vagal rebound. However, women given oxytocin reported more anger (e.g., mean change men = −0.62 vs. women = 0.71) and had better math performance following social stress.
Conclusion: Findings indicated that oxytocin stimulates an approach-oriented cardiovascular profile during social stress, suggesting mechanisms by which oxytocin might influence health. However, before considering oxytocin as therapeutic or uniformly beneficial, greater understanding of possible gender dimorphic effects is needed.

Keywords: oxytocin; social bonding; stress regulation; gender; health

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Peripheral oxytocin, social support and psychological functioning in a highly traumatized sample

Background: Oxytocin is associated with both social cognition/perception and affiliation and with stress response regulation. Both stress response regulation and social factors influence response to trauma. While some social/interpersonal factors may mitigate response to trauma (e.g., social support), others can contribute to trauma-related symptoms (e.g., interpersonal avoidance). While most research on the effects of oxytocin shows a positive influence on social cognition/affiliation, other research suggests that this influence varies with context (e.g., oxytocin is associated with decreased trust/affiliation in the context of social threat). Furthermore, some studies of endogenous oxytocin levels show positive relationship between with symptoms of trauma related disorders (e.g., depression and posttraumatic stress disorder (PTSD)).
Methods and results: We present data from a sample ($n = 90$) of highly traumatized adults living in an urban environment. Our data show a significant, positive relationship between plasma oxytocin levels and social support from family members ($p < 0.05$). However, we also found a significant, positive relationship between plasma oxytocin and symptoms of depression ($p = 0.04$) and PTSD ($p = 0.02$) and that the relationship of peripheral oxytocin and was strongest among those adults with a history of childhood maltreatment ($p < 0.05$).
Implications: We found that, in a highly traumatized sample, peripheral oxytocin was positively associated with both perceived social support and with levels of depression and PTSD. One way of understanding this data is the idea that oxytocin is associated with salience of social cues. In some circumstances (e.g., relationships with trusted family members), oxytocin may positively influence social perceptions/behaviors. In other circumstance (e.g., threatening interpersonal contexts), it may be a marker for trauma-related symptoms such a depression and PTSD. Many of our study participants live in unsafe neighborhoods and have been exposed to repeated interpersonal trauma. Interpersonal trauma, particularly in childhood, may increase the likelihood social cues are perceived as threatening. Thus, these data point to the need for complex models in understanding relationship of trauma response and oxytocin and in efforts to use oxytocin in the treatment of trauma exposed individuals.

Keywords: oxytocin; social support; stress response; trauma; PTSD; depression

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Intranasal oxytocin improves recall of autobiographical memories: a dose-response study

Rationale/statement of the problem: We previously found that the intranasal administration of oxytocin positively altered self-reported personality. Changes in self-perception may represent one mechanism by which oxytocin facilitates prosocial behavior. To follow up this finding, we explored the acute effects of two doses of intranasal oxytocin (24 IU or 48 IU) on autobiographical memory. We predicted that oxytocin would decrease participants' recall of overgeneral autobiographical memories (non-specific memories of the past) in a dose-dependent fashion. Since depressed individuals recall more overgeneral memories for past events, we hypothesized that the relation between oxytocin and autobiographical memory would be moderated by depressive symptoms.
Methods: Seventeen males self-administered a placebo or oxytocin on three separate occasions in a placebo-controlled, double-blind, and within-subjects experiment. Participants were administered the Autobiographical Memory Test (AMT) 110 min after drug administration.
Results: Participants recalled fewer overgeneral memories following the administration of 24 IU, but not 48 IU, of intranasal oxytocin relative to placebo [$pr^2 = .23$, $b = -0.824$, $t(15) = -2.426$, $p = .026$], and individuals with higher depressive symptoms exhibited this effect in greater magnitude [$pr^2 = .20$, $b = -0.148$, $t(15) = -2.285$, $p = 0.037$].
Conclusions: The findings suggest that a 24 IU dose of intranasal oxytocin alters the recall of personal past memories, which may be a mechanism by which oxytocin changes self-perceptions. This is one of the first dose-response studies on intranasal oxytocin, and our findings suggest lower doses of oxytocin may have greater beneficial effects in young adults presenting with high depressive symptoms.

Keywords: intranasal oxytocin; dose-response; 24 IU; 48 IU; depression; autobiographical memory

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Intranasal oxytocin attenuates the cortisol response to physical stress: a dose–response study

Rationale/statement of the problem: Intranasal oxytocin attenuates cortisol levels during social stress inductions. However, no research to date has documented the dose–response relationship between intranasal oxytocin administration and cortisol, and researchers examining intranasal oxytocin have not examined the cortisol response to physical stress. We, therefore, examined the effects of 24 and 48 IU of intranasal oxytocin on the cortisol response to vigorous exercise.
Methods: Seventeen males participated in a randomized, placebo-controlled, double-blind, and within-subject experiment. Participants engaged in vigorous exercise for 60 minutes following the administration of placebo or intranasal oxytocin on three occasions. Saliva samples and mood ratings were collected at 8 intervals across each session.
Results: Salivary cortisol concentrations changed over time, peaking after 60 minutes of exercise [Quadratic: $F(1,16) = 7.349$, $p = 0.015$, partial $\eta^2 = 0.32$]. The 24 IU dose of oxytocin attenuated cortisol levels relative to placebo [$F(1,16) = 4.496$, $p = 0.05$, partial $\eta^2 = 0.22$) and the 48 IU dose, although the latter fell just short of statistical significance [$F(1,16) = 3.054$, $p = 0.10$, partial $\eta^2 = 0.16$). There was no difference in the cortisol response to exercise in participants who were administered 48 IU of intranasal oxytocin relative to placebo. Intranasal oxytocin had no effect on mood.
Conclusion: This is the first study to demonstrate that the effect of intranasal oxytocin on salivary cortisol is dose-dependent, and that intranasal oxytocin attenuates cortisol levels in response to physical stress. Future research using exogenous oxytocin will need to consider the possibility of dose–response relations.

Keywords: intranasal oxytocin; cortisol; stress; exercise; 24 IU; 48 IU; dose-response

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Oxytocin, attachment and the shift from self to other

Background: Accumulating research indicates that oxytocin (OT) plays a key role in human social cognition and behavior. Inspection of the data, however, suggests that the social effects of OT often depend on contextual factors, including person characteristics. For example, some studies show that OT is helpful for avoidantly attached individuals, who are less socially engaged, whereas other studies show that OT exacerbates chronic interpersonal insecurities in anxiously attached individuals, who are preoccupied with closeness. Such variability raises questions about the mechanism by which OT influences human social behavior. Drawing upon animal research on OT and the other-directed (e.g., maternal) behavior, we propose that OT induces a similar shift in focus away from self and toward others in humans. This theory would explain some of the person-specific effects of OT since becoming more other- and less self-oriented should be helpful for avoidant individuals who are excessively focused on the self to the exclusion of others, but could be hurtful for anxious individuals who are already overly other focused and have no sense of self.
Methods: Thirty-one males received 24 IU intranasal OT/placebo in a randomized, double-blind, crossover trial and then completed tasks assessing the implicit cognitive accessibility and explicit self perceptions of agency (self orientation) and communion (other orientation). Individual differences in attachment were assessed at baseline.
Results: OT significantly decreased the cognitive accessibility of agency (self) and increased the cognitive accessibility of communion (other). Similarly, OT significantly decreased the endorsement of agency traits (arrogant) and increased the endorsement of communal traits (kind, warm, caring). Critically, this OT-induced shift from self to other differentially affected avoidant and anxiously attached participants, with avoidant individuals, who are generally low in communion, showing the largest increase in communion following OT, but anxious individuals, who are generally low in agency, showing even further reduction in agency/sense of self.
Conclusions: These data shed light on the variability in extant research on the social effects of oxytocin in humans and help explain both the beneficial and potentially harmful effects of OT.

Keywords: oxytocin; attachment; anxiety; avoidance; agency; communion

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The role of oxytocin at the interface of stress and social behavior

Background: The neuropeptide oxytocin (OT) is well known for its positive effects on dampening stress responses and increasing prosocial behavior. This view of OT has led to increased interest in its application for the treatment of a wide range of disorders that include autism, anxiety, trauma, and schizophrenia. However, paradoxical findings in recent work have revealed that OT may play a more nuanced role in regulating physiology and behavior. This work is beginning to shed new light on contextual factors that may influence the direction of OT's effects.
Methods: In the present study, we used female prairie voles (*Microtus ochrogaster*) to study the mechanisms through which OT pretreatment and a familiar social context interact to influence the response to a naturalistic stressor. Prairie voles were chosen as a model to examine interactions between stress and sociality because, such as humans, they exhibit vagal cardioregulatory dominance and selective preferences for familiar social partners.
Results: We found that OT pretreatment prior to a stressor was associated with changes in behavior, plasma hormone concentrations, and patterns of functional coupling between brain areas known to be critically involved in stress responses and social cognition.
Conclusion: This talk will discuss recent work, from our lab and others, that examines the role of OT at the interface of stress and social behavior.

Keywords: oxytocin; stress response; social behavior; animal study

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Epigenetic brain modifications associated with early-life adversity

Rationale/statement of the problem: Childhood maltreatment negatively impacts brain development, often producing transgenerational continuity of abusive parenting and increased risk for a range of psychiatric disorders. The biological basis for these far-reaching effects is not currently understood, but evidence suggests traumatic events could affect behavioral trajectories through changes in gene expression that are mediated by DNA methylation.
Methods: To explore this, we exposed male and female infant rats to nurturing or adverse caregiving environments. We measured changes in DNA methylation and gene expression in developing and adult animals. Candidate genes were selected according to their role in brain plasticity, responsiveness to stress, and association with several psychiatric disorders.
Results: Exposure to adverse caregiving environments induced long-lasting changes in cortical DNA methylation and expression of the brain-derived neurotrophic factor (BDNF) gene. In addition, females exposed to adverse caregiving environments later mistreated their own offspring, and their offspring likewise displayed altered DNA methylation. We are currently investigating the impact of nurturing vs. adverse caregiving environments on epigenetic gene regulation within a larger behaviorally relevant brain network (the medial prefrontal cortex, central/basolateral amygdala, dorsal vs. ventral hippocampus). Preliminary biochemistry data indicate caregiving experiences trigger epigenetic changes that differ between brain regions, sexes, and gene locus.
Conclusions: These findings demonstrate the remarkable ability of early-life caregiving environments to produce distinct epigenetic modifications across behaviorally relevant brain regions. Our work as well as that of others suggests that DNA methylation serves as a biological pathway linking early-life adversity to long-term (and perhaps multigenerational) changes in neurobiology and behavior.

Keywords: brain development; childhood maltreatment; gene expression; DNA methylation; BDNF

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Leptin deficiency in maltreated children

Background: Childhood maltreatment is linked to multiple metabolic and immunological abnormalities. Experimental research in animal models showed that stressful experiences in early life may also be associated with impaired leptin response to physiological stimuli, such as adiposity and inflammation. Therefore, we tested if maltreated children showed leptin deficiency.
Methods: We assessed leptin and C-reactive protein in dried blood spots and anthropometric measures from 170 twelve-year-old participants of the Environmental Risk (E-Risk) Study. Childhood maltreatment was prospectively assessed through repeated interviews with mothers in the first decade of study participants' life.
Results: Maltreated children showed a trend towards lower leptin levels than non-maltreated children. Furthermore, maltreated Children showed reduced leptin response to increasing inflammation and adiposity levels. These findings could not be explained by key potential confounders or pre-existing abnormalities in energy homeostasis.
Conclusions: Childhood maltreatment is associated with leptin deficiency, which could contribute to previously reported metabolic and immune abnormalities. Exposure to childhood trauma among pregnant women is associated with increased placental CRH production over gestation.

Keywords: childhood maltreatment; childhood trauma; stress; leptin; obesity; inflammation

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Exposure to childhood trauma among pregnant women is associated with increased placental CRH production over gestation

Rationale: Exposure to traumatic events, particularly during sensitive periods in childhood, is known to have persisting effects on health and disease risk in adult life. A few studies that have examined the course and outcome of later pregnancies in women with early trauma history bring up the intriguing possibility of transgenerational transmission of the effect of maternal childhood trauma on her developing fetus. However, the mechanism(s) underlying this effect have yet to be clarified. In humans and other higher primates, a stress-related system that is particularly relevant for key gestational processes, fetal development, and birth outcomes is placental corticotropin-releasing hormone (pCRH). In this study, we address the hypothesis that history of early life trauma is associated with variation in the level and trajectory of pCRH production over the course of human gestation.
Methods: A study population of sociodemographically and ethnically diverse women with singleton pregnancies ($N = 333$) provided information about childhood abuse and neglect (Childhood Trauma Questionnaire, or CTQ). Placental CRH levels were assessed prospectively at 1–5 time points over gestation (T1: mean = 15.0 weeks, SD = .72 until T5: mean = 36.5 weeks, SD = .78). Because of the expected exponential increase of pCRH production over gestation, pCRH values were log-transformed and Generalized Estimating Equation modeling was employed.
Results: One hundred thirty-seven women (41.1%) reported having experienced at least one type of trauma during childhood, and 75 (22.5%) reported exposure to multiple traumas. A higher childhood trauma score was significantly associated with higher pCRH levels over the entire period of gestation (Wald $\chi^2(1) = 4.68$, $p = .030$, $\beta = .005$). With the exception of physical and sexual abuse, this relationship was observed for all trauma subscales. The effect was dose dependent, with a higher number of different types of traumas being related to higher concentrations of pCRH.
Conclusion: To the best of our knowledge, this is the first report linking exposure to traumatic events in childhood with subsequent placental physiology, thus identifying a possible mechanism of transgenerational transmission. Given the importance of placental CRH in primate pregnancy, this finding also may have appreciable clinical significance.

Keywords: childhood trauma; placental CRH; pregnancy; maternal life course history

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Child abuse moderates cortisol s relationship to memory

Background: Early life stress restructures the nervous system. In rodents, the level of maternal care causes lifelong differences in central glucocorticoid (GC) sensitivity and memory. Furthermore, human adults with a history of child abuse have decreased hippocampal GC receptor gene expression and lower cortisol responses to stress. As GCs modulate memory, hypothalamic–pituitary–adrenal (HPA) axis functions altered by atypical care may influence memory.
Methods: Participants were women ($N = 55$) reporting no-to-minimal abuse (no maltreatment group) on the Child Trauma Questionnaire and those reporting clinically significant sexual or physical abuse (abuse group). Participants completed the Beck Depression Inventory (BDI), as depression is more prevalent in child abuse survivors and is known to impact cortisol levels. Participants then completed the Emotional Picture Memory Task. During encoding, participants viewed pictures composed of negative or neutral emotionally valenced objects and backgrounds. In a surprise retrieval test, participants indicated if objects and backgrounds presented separately were the same, similar, or new to those viewed earlier. Saliva samples were collected to measure basal (unstressed) cortisol levels. Analyses focused on ''gist'' memory, and the percentage of responses when an object viewed previously was classified as similar or the same. Higher cortisol has been tied to better gist memory.
Results: Abuse history moderated cortisol's effect on gist memory, $\beta = -0.557$, SE = 0.212, $p < 0.01$. When controlling BDI, cortisol negatively correlated with memory in the abuse group and positively correlated with memory in the no abuse group.

Conclusions: These findings are particularly compelling as the abuse group result contrasts with previous human memory and rodent research. However, basal vs. stress-induced cortisol may differentially affect memory. Furthermore, child abuse is likely a more profound early stressor compared to maternal neglect in rodents. In conclusion, early experience shapes how GCs affect cognitive functioning. This study is an essential step toward determining physiological and long-term effects of child abuse.

Keywords: glucocorticoids; memory; early life stress; salivary cortisol; HPA axis

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Childhood adversity and inflammatory processes in youth: a prospective study

Rationale/statement of the problem: Retrospective studies show that childhood adversity is associated with systemic inflammation in adulthood. Few prospective studies have examined whether childhood adversity influences inflammation in an observable manner during childhood or adolescence and whether these effects are sustained over time.
Methods: Using longitudinal data from the Avon Longitudinal Study of Parents and Children, we examined associations between acute adverse events at seven time points prior to age 8 and inflammation at ages 10 and 15. Inflammatory markers at age 10 included interleukin-6 (IL-6; $N = 4{,}655$) and C-reactive protein (CRP; $N = 4{,}647$), and CRP was measured again at age 15 ($N = 3{,}286$). We further evaluated whether body mass index (BMI), depression, or cigarette smoking mediated associations between adverse events and inflammation.
Results: Adverse events in middle childhood (occurring between ages 6 and 8), as well as cumulative adversity between the ages of 1.5 and 8 years, were associated with higher levels of IL-6 and CRP at age 10. Adverse events occurring in early childhood (age 1.5) or middle childhood (age 8), and cumulative adversity between the ages of 1.5 through 8 years predicted increased levels of CRP at age 15, and these associations persisted after adjustment for CRP at age 10. Some, but not all, of these associations were mediated by BMI.
Conclusions: This study documents that exposure to adverse events prior to age 8 is associated with elevated inflammation at age 10 and in mid-adolescence. These findings provide prospective evidence for a biological mechanism by which early experiences may shape long-term health.

Keywords: children; adolescents; youth; inflammation; C-reactive protein; interleukin-6; stressful life events; prospective cohort

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Hypothalamic-pituitary-adrenal axis and memory in PTSD

Rationale/statement of the problem: In posttraumatic stress disorder (PTSD), enhanced negative feedback of the hypothalamic-pituitary-adrenal axis is a prominent finding, which has often been interpreted in the context of enhanced glucocorticoid receptor sensitivity. Neuropsychological alterations are also an important feature in PTSD. Problems particularly with learning and memory have been found, including deficits in verbal declarative memory as well as autobiographical memory. In healthy humans, most studies suggest impairing effects of glucocorticoids on memory retrieval. Up to now, studies that investigate the effects of cortisol administration on memory in patients with PTSD are rare and yielded inconclusive results.
Methods: In a placebo controlled cross-over study, we compared the effect of exogenous cortisol on memory retrieval in patients with PTSD ($N = 44$) with the effects in healthy controls ($N = 65$).

Results: Opposing effects of cortisol on memory were observed when comparing patients with controls. In controls, cortisol had impairing effects on memory retrieval, whereas in patients with PTSD cortisol had enhancing effects on memory retrieval.
Conclusion: The present results suggest beneficial effects of acute cortisol elevations on hippocampal mediated memory processes in PTSD. Possible neurobiological mechanisms underlying these findings are discussed.

Keywords: HPA-axis; PTSD; declarative memory; cortisol; autobiographical memory

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Association of posttraumatic stress disorder with increased prevalence of autoimmune disorders in Iraq and Afghanistan veterans

Rationale: Accumulating evidence links posttraumatic stress disorder (PTSD) with elevated inflammatory activity. However, the clinical significance of this association is unclear. Although inflammation could increase the risk of autoimmune disease, little is known about whether patients with PTSD are at increased risk of developing autoimmune disorders.
Methods: We conducted a retrospective cohort study of 673,277 Iraq and Afghanistan veterans younger than 55 years, who received VA healthcare from October 1, 2005, to March 31, 2012, with at least 1 year of follow-up. Department of Veterans Affairs administrative data were used to identify ICD-9 codes for mental health and autoimmune disorders and to obtain sociodemographic, military service, and health service utilization information. Generalized linear models were used to ascertain the association of PTSD with subsequent autoimmune diagnoses after adjusting for age, race, and number of primary care visits.
Results: The sample was 88% male and 49% white with a mean age of 31.3 years ($\pm$8.7). PTSD was diagnosed in 206,623 (31%) veterans, and mental health disorders other than PTSD were diagnosed in an additional 132,242 (20%) veterans. Compared to veterans with no mental health diagnoses, those diagnosed with PTSD had increased risk for subsequent diagnosis with thyroiditis (adjusted relative risk [ARR] = 1.74; 95% CI 1.67, 1.82), rheumatoid arthritis (ARR = 1.92; 95% CI 1.67, 2.20), inflammatory bowel disease (ARR = 1.32; 95% CI, 1.20, 1.46), multiple sclerosis (ARR = 2.23; 95% CI, 1.88, 2.64), systemic lupus erythematous (ARR = 1.81; 95% CI, 1.48, 2.23), and any of these disorders alone or in combination (ARR = 1.50; 95% CI, 1.45, 1.56). Moreover, while there was an increased risk for each of these disorders in veterans with mental health disorders other than PTSD, the risk was consistently higher in those diagnosed with PTSD. Women had significantly higher risk for autoimmune disorders overall, but the pattern of results was similar in men and women.
Conclusion: Veterans with PTSD appear to be at increased risk for autoimmune disorders compared to those with no or other mental health diagnoses. Future prospective longitudinal cohort studies are needed to establish causality, measure inflammatory markers in conjunction with PTSD, and evaluate whether successful treatment of PTSD reduces risk of autoimmune disorders.

Keywords: autoimmune disorders; inflammation; post-traumatic stress disorder; psychiatric disorders; traumatic stress; veterans

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Evidence for epigenetic alterations in PTSD

Rationale/statement of the problem: Neuropeptide Y (NPY) is a peptide with behaviorally relevant effects on the hippocampus and is thought to function as an endogenous anxiolytic. In prior work, we reported that veterans

who had recovered from combat-related post-traumatic stress disorder (PTSD) had higher levels than those who were not combat exposed. NPY levels were significantly associated with the extent of symptom improvement, suggesting that plasma NPY levels may represent a biological correlate of resilience to, and/or recovery from, the adverse effects of trauma exposure. Cytosine methylation of the glucocorticoid gene (GR methylation) has been associated with PTSD risk and/or symptom expression. GR methylation is influenced by environmental factors that can result in enduring differences in function, including neuroendocrine regulation. As the NPY gene has glucocorticoid response elements, levels of circulating NPY represent a potential indicator of alterations in GR responsivity.

Methods: The relationship of NPY to PTSD and GR methylation was examined in two samples. In the first sample, veterans who developed PTSD following combat exposure were compared to those who did not develop PTSD. In a second sample, veterans with combat-related PTSD were assessed prior to and following a course of prolonged exposure (PE).

Results: In the cross-sectional study, veterans with PTSD had higher NPY levels than those who never developed PTSD (t (62) = −1.99, p =0.05; 95.8±45.6 pm/l vs. 73.9±41.5 pm/l). NPY associated with number of GR methylated sites in the full sample (r =0.35, n =64, p =0.005), but not with average percent methylation (r = −0.05). When the associations were examined separately by PTSD group status, results showed a positive association between NPY and number of methylated sites (r =0.36) as well as percent methylation (r =0.38) in veterans with PTSD. However, NPY was only associated with the number of methylated sites (r =0.35) in the subjects who did not develop PTSD following combat exposure. In the treatment study, plasma NPY levels increased among veterans who responded to treatment (who no longer met diagnostic criteria for PTSD following PE), compared to treatment non-responders, as indicated by a significant group æ time interaction (F1,14 =5.48, p =0.035). While plasma NPY was comparable in the two groups at pretreatment (responders: 71.4±20.3 pm/l, non-responders: 71.0±16.0 pm/l), responders had higher plasma NPY (84.0±24.2 pm/l) relative to non-responders (61.0±15.4 pm/l). Both pretreatment number of GR methylated sites (r =0.53, (n = 16, (p =0.04) and average percent GR methylation (r =0.75, (n =15, (p =0.001) were associated with higher plasma NPY at post-treatment.

Conclusion: To the extent that improvement from symptomatic PTSD may involve a mobilization of endogenous mechanisms to reduce hyperarousal and other post-trauma sequellae, the results of these studies are consistent in suggesting a role for NPY. NPY was elevated in a sample of combat veterans with PTSD, and increased in association with PTSD improvement in response to trauma-focused treatment. GR methylation was associated with combat-related PTSD in a cross-sectional study, and with treatment associated improvement in PTSD. These findings suggest that epigenetic modification of the GR gene may be associated with resilience in PTSD.

Keywords: Glucocorticoid receptor; neuropeptide Y; PTSD, methlylation; prolonged exposure

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A randomized, double-blind, placebo-controlled, crossover trial of mifepristone in Gulf War veterans with chronic multisymptom illness

Background: Nearly 34–65% of Gulf War veterans (GWV) continue to suffer from chronic multisymptom illness (CMI); novel pharmacological treatment approaches are needed to improve the health of these veterans. This study aims to determine whether mifepristone, a glucocorticoid receptor antagonist, can reverse the neuroendocrine alterations described in GWV and improve the physical health, mental health, and neurocognitive functioning of GWV with CMI.

Methods: Sixty-five GWV were enrolled into the study; 36 eligible GWV who met criteria for CMI and did not have any exclusionary medical or psychiatric conditions were randomized to receive mifepristone (200 mg/day) or matched placebo first in this crossover study. Both treatment phases lasted 6 weeks and were separated by a 4-week wash-out period. The primary clinical outcome measure was the change from treatment baseline to treatment endpoint in the physical health component score (PCS) of the veterans SF-36 health survey. Primary neurocognitive outcome measures included change in spatial working memory and verbal declarative memory as measured by the MATRICS Consensus Cognitive Battery. Additional outcome measures included change in

the mental health components score (MCS) of the SF-36 and self-reported symptoms of fatigue, depression, and PTSD. Cortisol and ACTH levels and a measure of glucocorticoid sensitivity (lysozyme $IC_{50\text{-}DEX}$) were also obtained to characterize the neuroendocrine response to mifepristone in GWV with CMI.
Results: Data collection is complete; results regarding the primary and secondary clinical, neuropsychological, and neuroendocrine outcome measures will be presented.
Conclusion: If this study shows that mifepristone improves physical health or cognition or reduces constituent symptoms of CMI in GWV, it would suggest that mifepristone may be of therapeutic value in this population.

Keywords: mifepristone; Gulf War veterans; chronic multisymptom illness; therapy

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Evidence for distinct biological perturbations in PTSD with severe child abuse: implications for PTSD biomarkers

Rationale/statement of the problem: Evidence for distinct biological perturbations in posttraumatic stress disorder (PTSD) with severe child abuse versus no child abuse: consequences for robust biomarkers for PTSD. The identification of biomarkers for PTSD has been difficult, likely due to inter-individual differences in genetic risk factors and environmental exposures. The aim of the current study was to interrogate the influences of the environment on gene expression profiles by characterizing biological differences in PTSD after severe child abuse versus PTSD after adult trauma.
Methods: A total of 396 trauma-exposed individuals were included in this study. The PTSD symptomatic scale (PSS), clinician-administered PTSD scales (CAPS), childhood trauma questionnaire, and trauma events inventory were used to assess current clinical PTSD and childhood and adult trauma severity. Whole blood gene expression and DNA methylation was measured on Illumina Human-HT12v3 and Human Methylation 450k arrays. Analysis was performed by using R software.
Results: Of 741 transcripts significantly associated with current PTSD severity, only 2% was associated with PTSD in both, individuals exposed to child abuse and adult trauma ($N=32$) and individuals exposed to adult trauma only ($N=29$), after accounting for adult trauma severity. Expression differences were also reflected in DNA methylation differences between the groups. Functional annotations revealed distinct biological pathways enriched among the expression profiles associated with PTSD in these two groups.
Conclusion: These data suggest that PTSD occurring after severe child abuse is biologically distinct from PTSD after adult trauma, therefore, accounting for different environmental variables is crucial for identification of biomarkers for PTSD.

Keywords: PTSD; child abuse; trauma; gene expression; methylation

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Evidence for acute central sensitization to prolonged experimental pain in subjects with PTSD

Statement of the Problem: Pain and posttraumatic stress disorder (PTSD) are highly comorbid conditions. Patients with chronic pain have higher rates of PTSD. Likewise, patients with PTSD are often diagnosed with numerous chronic pain conditions. Despite the high pain-PTSD comorbidity, the pathophysiologic mechanisms underlying this phenomenon are incompletely understood and only recently researchers have started to investigate pain-PTSD overlap using experimental pain models. The aim of the present study was to examine the activation of the pain-processing pathway in a cohort of combat PTSD compared to combat controls in response to a prolonged painful stimulus.
Methods: Novel data from the experimental pain model using intramuscular capsaicin comparing a group of 10 Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans with combat-related PTSD and 11 matched OEF/OIF veterans without PTSD will be presented. Intramuscular capsaicin causes a prolonged,

deep-aching muscle pain, resembling pain associated with chronic pain states. Following capsaicin injection into the left thigh muscle, subjects underwent functional magnetic resonance imaging scanning while whole brain perfusion was measured with arterial spin labeling (ASL). At every 10 min, samples of cerebrospinal fluid (CSF) were drawn and subjective pain ratings were measured throughout the scanning window (30 min). Following scanning, CSF draws and pain ratings continued and evidence for central sensitization was assessed by temporal summation of repeated pressure pain stimuli.
Results: Our results show evidence for an acute form of central sensitization in the PTSD group in comparison to matched combat controls. The maximum pain response and initial pain decrease were not different between the two groups, yet significantly higher pain ratings were observed in the PTSD group 15 min postinjection of capsaicin. ASL showed significant group by time interactions within pain-processing network, whereby PTSD group maintained high levels of brain perfusion in the ventral medial frontal gyurs and other interoceptive and evaluative brain circuits throughout the second half of the scan, similar to subjective pain ratings. Furthermore, significantly higher temporal summation of pain was also noted in the PTSD compared to the control group.
Conclusion: We found increased sensitivity to prolonged, deep experimental pain in combat-related PTSD compared to traumatized subjects who never developed PTSD following combat. We posit that this increased pain response on behavioral, spinal, and supraspinal levels is related to a form of acute central sensitization in these individuals in response to a prolonged pain stimulus. Initial neuroimaging findings point to differential activation of frontal systems as potentially underlying pain-PTSD pathways and perhaps provide initial mechanisms for the development of testable models of perturbed pain processing in PTSD.

Keywords: PTSD; pain; capsaicin; sensitization; fMRI

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The longitudinal course of posttraumatic sensitization disorder

The gradual emergence of symptoms following exposure to traumatic events has presented a major conceptual challenge to psychiatry. The presumption that all people have significant acute symptoms is not supported by careful longitudinal research. One such study of 1,018 accident victims conducted over 2 years will be presented. The mechanism that leads to the progressive escalation of symptoms with the passage of time leading to delayed onset post-traumatic stress disorder (PTSD) involves the process of sensitisation and kindling. The acute stress response represents the neurobiological platform for the different trajectories of symptoms, and data on 49 participants will be presented, demonstrating how the acute hypothalamic–pituitary–adrenal axis reactivity and melatonin levels predict later symptoms.
The development of traumatic memories at the time of stress exposure represents a major vulnerability through repeated environmental triggering of the increasing dysregulation of an individual's neurobiology. An increasing body of evidence demonstrates how the increased allostatic load associated with PTSD. This broader perspective has important implications for developing treatments that address the underlying dysregulation of cortical arousal and neurohormonal abnormalities, following exposure to traumatic stress.

Keywords: PTSD; longitudinal course; vulnerability; allostatic load; treatment

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Longitudinal studies of trauma in police officers

Background: Results will be presented on a prospective longitudinal study of risk and resilience for post-traumatic stress disorder (PTSD) symptoms in 400 police academy recruits, assessed during academy training and followed during the first 7 years of police service.
Methods: Utilizing Latent Growth Mixture Modeling (LGMM) we have established three symptom trajectories, highly resilient, initially distressed with gradual improvement, and increasing distress.

Results: We will present findings on the relations of the following predictors ascertained during academy training to the three PTSD symptom trajectories: I.Q., family histories of anxiety, depression, alcohol and drug abuse, neuroticism, personal histories of childhood or adolescent traumatic exposure, levels of awakening cortisol, fear-potentiated acoustic startle, MHPG and cortisol responses to a critical incident video challenge, sleep quality as measured by actigraphy, and candidate polymorphisms including serotonin transporter (SLC6A4), adrenergic pathway genes, ADRB1, ADRB2, ADRA2C, brain derived neurotrophic factor gene (BDNF), genes for several critical components of the hypothalamic–pituitary–adrenal (HPA) axis such as the glucocorticoid receptor (NR3C1), CRH receptor 1 (CRHR1), and FK506 binding protein 5 (FKBP5) and Catechol-*O*-methyltransferase (COMT).
Conclusion: Mulivariate models of risk and resilience will be presented utilizing a multinomial logistic regression nested in the unconditional LGMM.

Keywords: stress; resilience; PTSD; cortisol; startle; MHPG; FKBP-5

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Altered functioning of the glucocorticoid receptor pathway is a vulnerability factor for development of PTSD symptomatology in response to military deployment to Afghanistan

Rationale: PTSD is associated with changes in the glucocorticoid receptor (GR) pathway. We hypothesized that altered functioning of the GR pathway is already present before development of PTSD and thus represents a biological vulnerability factor for the development of PTSD. Therefore, we investigated the predictive value of several GR pathway components for the development of high levels of PTSD symptoms.
Methods: We included a cohort of 1,032 Dutch soldiers prior to deployment to Afghanistan. GR pathway components were assessed in blood collected prior to deployment. PTSD symptoms were assessed 6 months after return.
Results: A high GR number, high GILZ mRNA expression, and low FKBP5 mRNA expression in leukocytes prior to deployment were independently associated with development of high levels of PTSD symptoms. In addition, sensitivity of T-cells for regulation by the synthetic glucocorticoid dexamethasone was associated with development of high levels of PTSD symptoms. However, the direction of the association between dexamethasone-sensitivity and PTSD depended on the presence of co-morbid depressive symptoms.
Conclusions: Altered functioning of the GR pathway in leukocytes is a vulnerability factor for development of high levels of PTSD symptoms. The identification of such biological vulnerability factors for PTSD could facilitate the selection of individuals for preventive treatment within groups at risk for trauma-exposure.

Keywords: PTSD; glucocorticoid receptor; FKBP5; dexamethasone; biomarker; vulnerability; military

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Prospective assessment of psychophysiological risk factors for PTSD

Rationale/statement of the problem: There is an urgent need to develop biological and behavioral predictors of PTSD risk/resilience in individuals with high trauma exposure, such as active military duty. First, we will briefly review psychophysiological risk factors for PTSD. Second, we will describe preliminary data from a prospective study of active duty Marines examining psychophysiological responses before and after deployment to Iraq or Afghanistan. Third, we will discuss our cross-species work in animal models of PTSD risk/resilience to inform these study findings.

Methods: This study was conducted as part of a 4 h battery (clinical, psychosocial, laboratory, and psychophysiological assessments) conducted both before, and 3 and 6 months after deployment (Marine Resiliency Study) in >2,500 Marines. Here, we examined (1) effect of deployment overall on physiological reactivity measures on baseline startle, pre-pulse inhibition, and affective modulation of startle and (2) comparison of pre-deployment startle reactivity across subjects matched for combat exposure with and without PTSD symptoms, 3 months post-deployment.
Results: We observed small but significant increases in baseline startle and pre-pulse inhibition after deployment. Startle potentiation to aversive images was also significantly increased after deployment. Importantly, baseline startle magnitude *before* deployment was significantly greater in subjects that went on to develop PTSD symptoms after deployment compared to their combat-matched controls.
Conclusions: These results support previous reports suggesting that startle reactivity may probe trait biological processes that confer risk for PTSD symptoms. To complement these findings, we (1) are conducting a similar prospective study to determine if fear conditioning and extinction performance predicts deployment-related stress disorders and (2) have developed a homologous rodent model to aid identification of potential epigenetic mechanisms underlying psychophysiological and fear-processing risk factors.

Keywords: PTSD; psychophysiological risk; prospective study; pre-pulse inhibition; startle; fear conditioning

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Glucocorticoids in hair as biomarkers of traumatization in healthy individuals and PTSD patients

While posttraumatic stress disorder (PTSD) and traumatization have frequently been associated with altered activity of the hypothalamic-pituitary-adrenal axis, specific results on changes in cortisol secretion have been relatively inconsistent. Amongst other things, this may be because of (i) limitations of previous methods for the assessment of long-term cortisol secretion as well as (ii) differences in the composition of the control group in which traumatized and non-traumatized individuals are often not distinguished. The current study aimed to address these problems by using assessments of glucocorticoids in hair as a measure of cumulative hormone secretion over prolonged periods of time and by carefully distinguishing between traumatized and non-traumatized controls. Data were obtained from 28 PTSD patients, 27 traumatized healthy controls, and 32 non-traumatized controls. Concentrations of cortisol (F) and cortisone (E) in proximal 3 cm hair segments were determined via LC-MS/MS. In addition, the severity of PTSD symptoms, the number of different lifetime-traumatic events, chronic stress, and depressiveness were measured. Results revealed that PTSD patients and traumatized healthy controls exhibited lower hair F and E levels compared to those of non-traumatized controls ($p < 0.05$, for both). Furthermore, negative correlations between hair F levels and symptoms of intrusion ($r = -0.34$, $p = 0.02$) and the number of different traumatic events ($r = -0.36$, $p = 0.01$) were found in traumatized individuals. The current results suggest that trauma exposure may be a critical factor influencing long-term endocrine alterations, which can be observed even in otherwise healthy and non-psychopathological individuals.

Keywords: posttraumatic stress disorder; traumatization; cortisol; cortisone; hair

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